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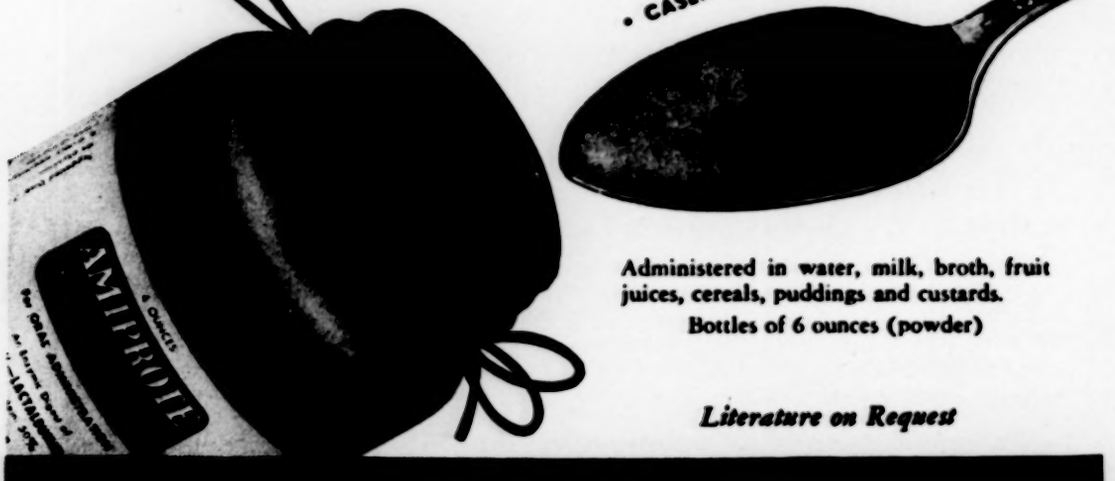

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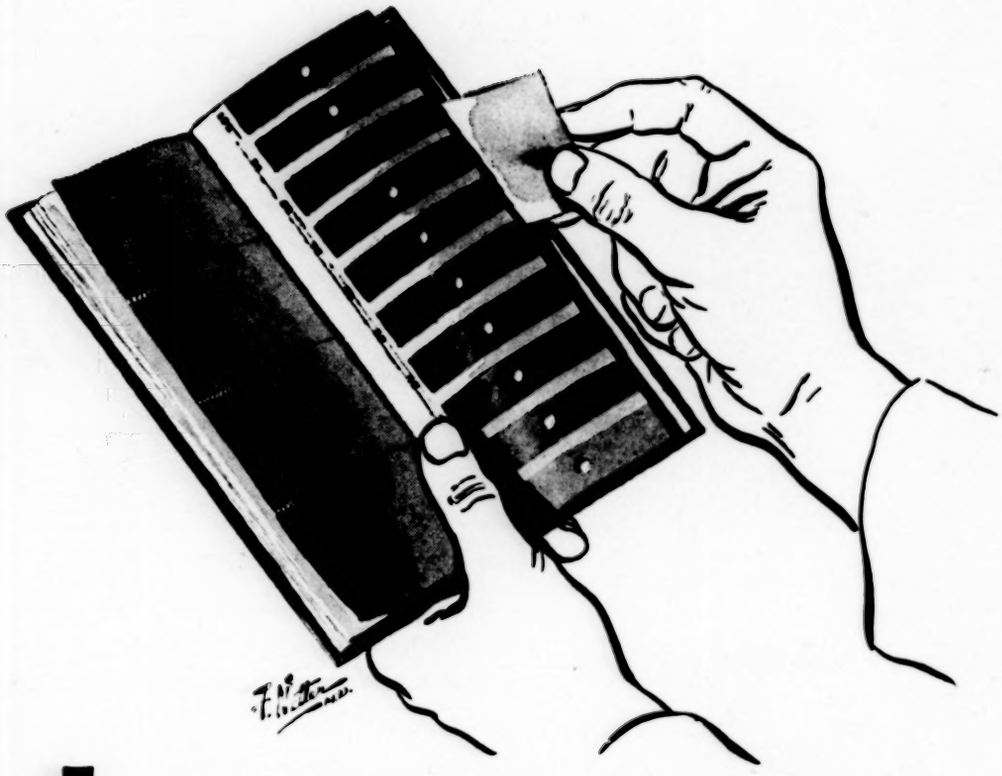

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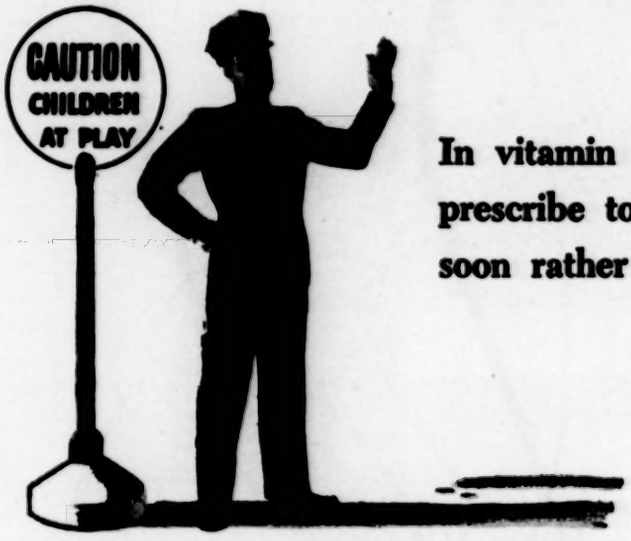

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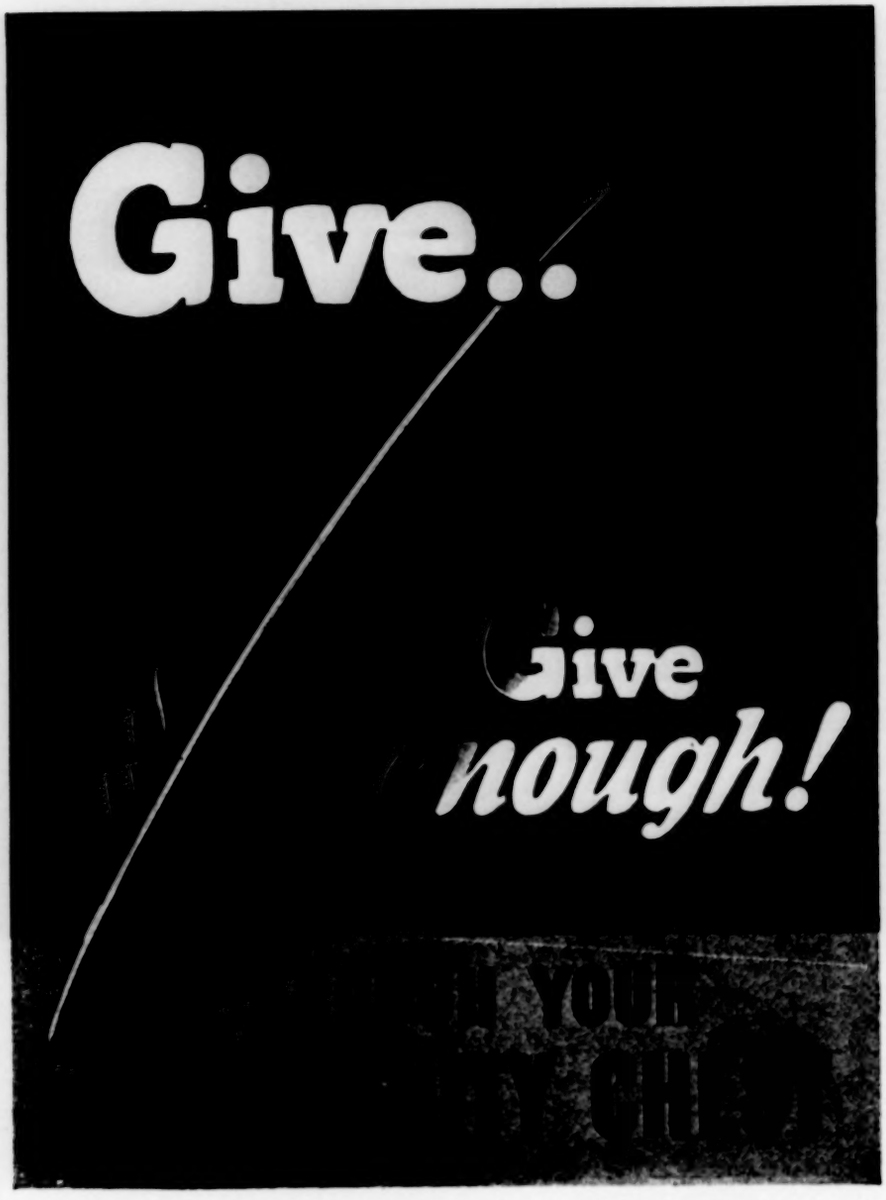
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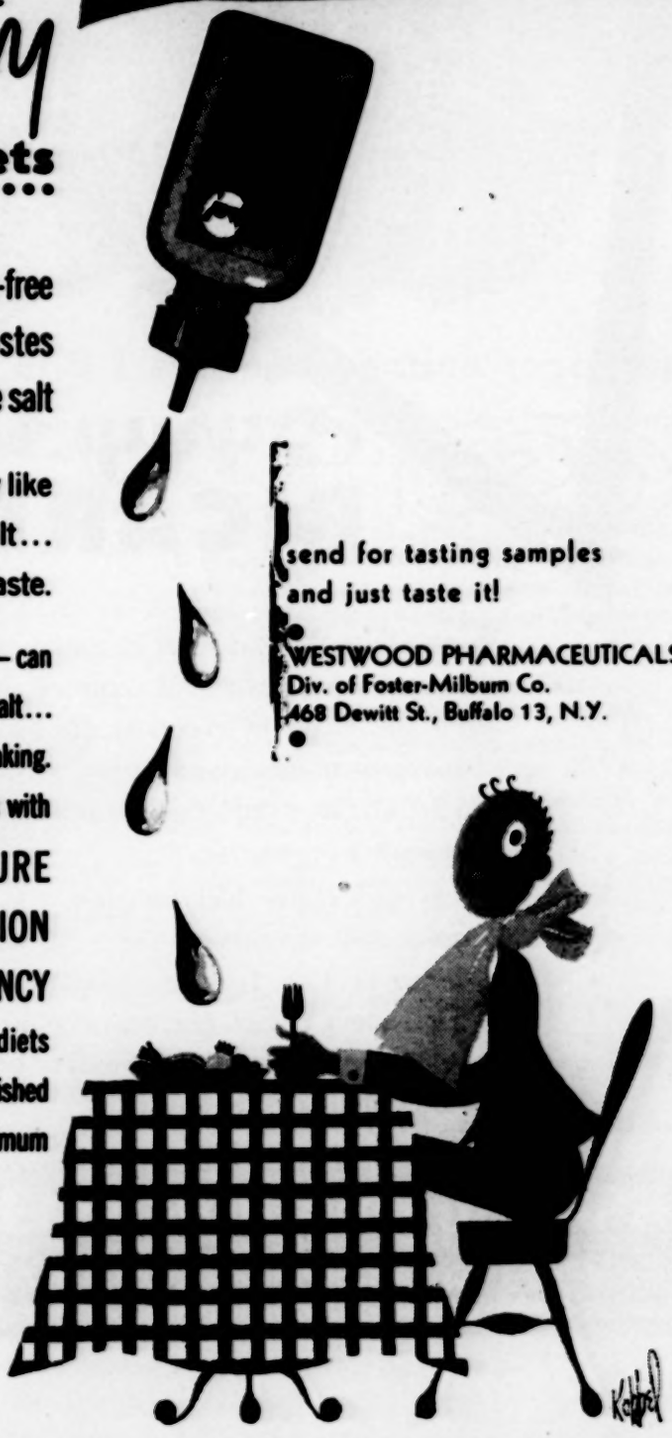

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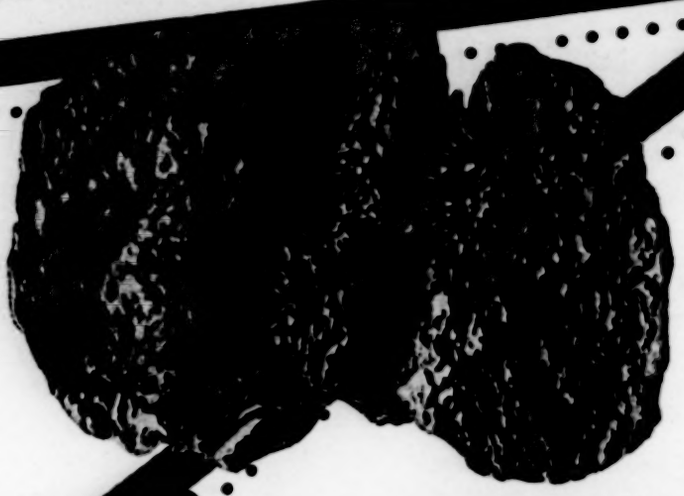

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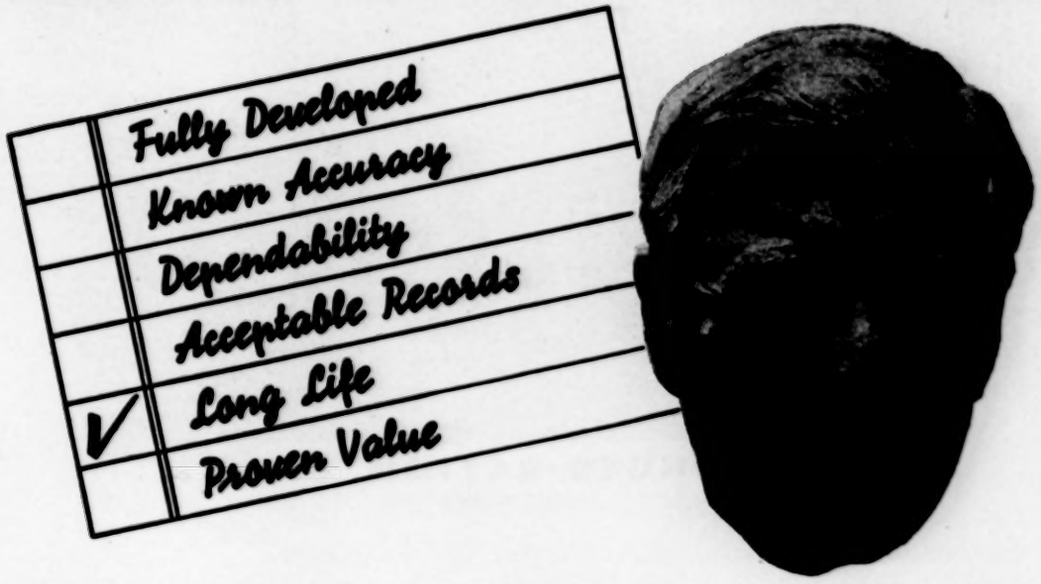

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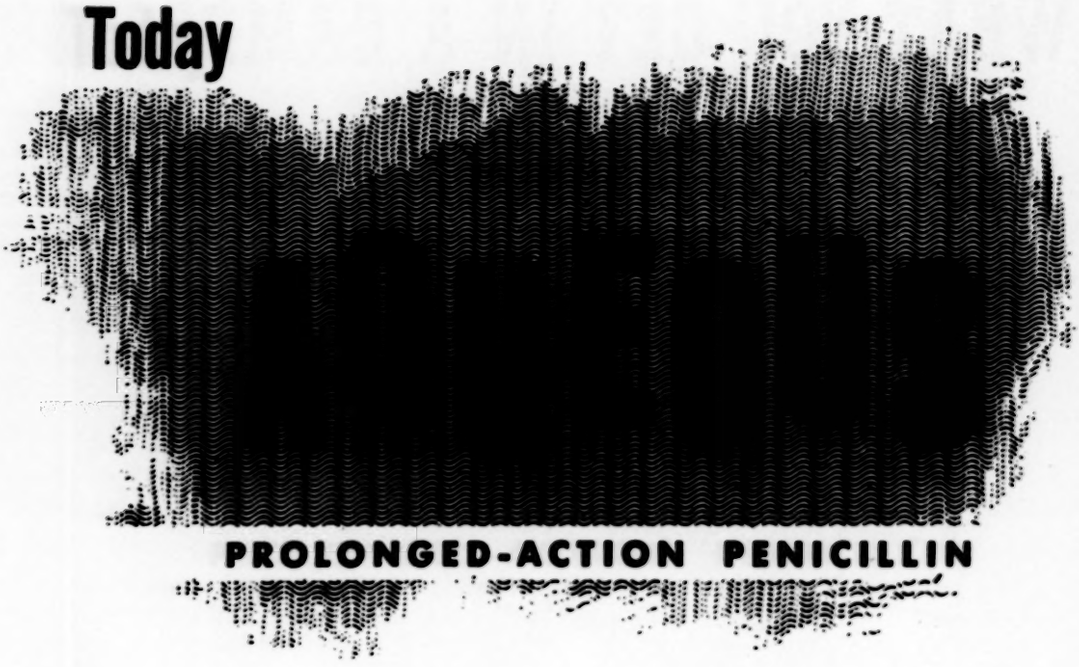

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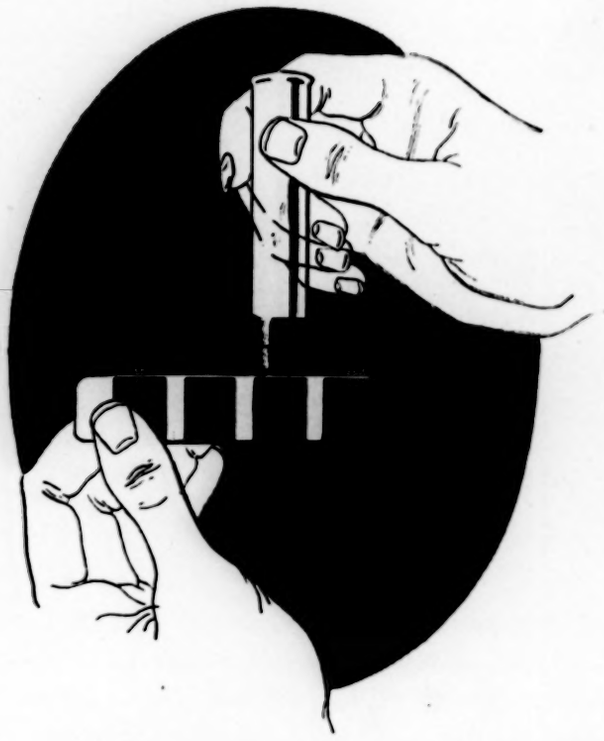

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The American Journal of Medicine

VOL. V OCTOBER, 1948 No. 4

Editorial

"Intractability" in Peptic Ulcer

THE term "intractable" so frequently used in reference to peptic ulcer is difficult to define. It may refer to the patient, to the ulcer or to complications present. Ordinarily, however, it is used to indicate that the symptoms of ulcer have not been relieved by or have recurred after the use of various therapeutic procedures, usually medical, sometimes surgical. The persistence or reappearance of symptoms is accompanied as a rule by objective roentgenologic or gastroscopic demonstration of the ulcer. Two or three questions inevitably arise: Why they fail to heal? Why the recurrence? Why the refractoriness?

These questions are, of course, inseparable from the basic one of the cause of peptic ulcer and from the still older question asked by John Hunter[1] of why the stomach does not digest itself. Many details of these phenomena are still unclear, but it is evident that one of the most important factors in the protection of the normal mucosa is the layer of mucus, constantly secreted and renewed. It is also clear that the cause of peptic ulcer, long thought to be unknown, is indeed of "peptic" origin, that it results from the inability of the mucosa to withstand digestion. Very little is known regarding the mucosal factors involved in this process although Konjetzny[2] and Büchner[3] form quite differing points of view and with conflicting concepts have both described quite well the histologic manifestations. Wangensteen[4] and his associates have shown that various factors, namely, posthemorrhagic anemia, shock, hemoconcentration, muscular fatigue, age, etc., abet the formation of experimental histamine ulcers in dogs. The extent to which these experiments may be translated into clinical equivalents is perhaps debatable but the principles established do seem valid. Wolf and Wolff[5] observed that in the human stomach with increased vascularity and turgor the surface of the mucosa became more friable and susceptible to injury. This vascularity could be produced in various ways including emotional conflict and frustration. There are doubtless many factors which reduce the susceptibility of the mucosa to digestion. Some of these may explain such phenomena as the location of the lesion, the tendency to recurrence at the same point, the seasonal variation and the precipitating effect of fatigue, emotional stress and infection. However, the feasibility of controlling these mucosal factors by clinical methods seems

[1] HUNTER, J. On digestion of the stomach after death. *Phil. Tr. Roy. Soc.*, 62: 447, 1772.

[2] KONJETZNY, G. Die entzündliche Grundlage der Geschwürsbildung im Magen und Duodenum. Berlin, 1930. Julius Springer.

[3] BÜCHNER, F. Die Pathogenese der peptischen Veränderungen. Jena, 1931. Gustav Fischer.

[4] FRIESEN, S. R. and WANGENSTEEN, O. H. Role of hemoconcentration in production of gastric and duodenal ulcer following experimental burns. *Proc. Soc. Exper. Biol. & Med.*, 64: 81, 1947.

LILLEHEI, C. W. and WANGENSTEEN, O. H. Effect of muscular fatigue on histamine-provoked ulcer with observations on gastric secretion. *Ibid.*, 67: 49, 1948.

LILLEHEI, C. W., DIXON, J. L. and WANGENSTEEN, O. H. Relation of anemia and hemorrhagic shock to experimental ulcer production. *Ibid*, 68: 125, 1948. Effect of age on histamine induced ulcers. *Ibid*, 68: 129, 1948.

[5] WOLF, S. and WOLFF, H. G. Human Gastric Function, An Experimental Study of a Man and His Stomach. New York, 1943. Oxford University Press.

rather doubtful. Clinicians from Sippy on have, therefore, concentrated upon measures to decrease the acid-pepsin attack rather than hypothetic schemes for protecting the mucosa or increasing mucosal resistance.

Through the years there have been students of the ulcer problem who have been unwilling to accept the validity of the concept enunciated by Schwartz[6] in 1910 of "no acid, no ulcer." Their voices have gradually been stilled as it has become established that chronic peptic ulcer occurs only in association with acid gastric juice. If a patient with peptic ulcer develops persistent achlorhydria spontaneously or after roentgen irradiation or as a result of surgery, the ulcers invariably heal and do not recur until or unless the acid gastric secretion returns.[7] This fact has led Wangensteen[8] to characterize the concept of "intractable ulcer" as a myth; because if sufficient stomach is removed surgically to produce permanent achlorhydria, the lesions do not recur.

This brings us back to the question of why some individuals develop peptic ulcer and others do not. Is the fault one of deficient mucosal resistance or of hypersecretion or are both factors operative? Levin's[9,10] studies have shown clearly that with respect to duodenal ulcer there is a profound increase in the fasting or basal gastric secretion of hydrochloric acid. While fasting, normal individuals secrete an average of approximately 680 mg. of hydrochloric acid in twelve hours whereas patients with duodenal ulcer yield an average return of 2,240 mg. In "intractable" ulcers Kirsner and Levin[11] have found the fasting output of hydrochloric acid to be as high as 6,353 mg. in twelve hours. This hypersecretion, as Dragstedt[12] has shown, is chiefly vagal in origin and can be profoundly reduced by complete bilateral vagotomy; subsequent healing of the ulcer occurs. In gastric ulcer the secretory situation is quite different[10] for the output of hydrochloric acid is not greater than that found in normal individuals. Acid gastric juice is invariably present but not in excessive amounts; in fact, there is frequently a definite hyposecretion. It seems evident, therefore, that in gastric ulcer the primary defect is probably one of decreased mucosal resistance arising in some unknown manner: decreased secretion of mucus in a particular area, excessive friability, accidental traumatic mechanical injury of the superficial mucosal cells or some such phenomenon. In the absence of acid gastric juice such erosions heal promptly; in the presence of acid chyme the regenerative power of the mucosa is still sufficient to bring about healing in the great majority; in a relatively small number peptic digestion transforms the erosion into an ulcer which gradually increases in size and depth. The process may stop at any point for the healing tendency of the mucosa is ever present.

Sippy[13] considered "the greatest known hindrance to the healing of the peptic ulcer . . . (to be) the disintegrating and digestive action of the gastric juice." We now know

[6] Schwartz, K. Ueber penetrierende Magen und Jejunalgeschwüre. *Beitr. z. klin. Chir.*, 67: 96, 1910.

[7] Palmer, W. L., Ricketts, W. E. and Hamann, A. The effect of achlorhydria upon the course of chronic peptic ulcer. *Tr. A. Am. Physicians*, 1948 (in press). Achlorhydria and peptic ulcer: A further study of the role of peptic activity in the pathogenesis and course of peptic ulcer. *Ann. Int. Med.*, 1948 (in press).

[8] Wangensteen, O. H. The ulcer problem. *Canad. M. A. J.*, 53: 309, 1945. Causes of failure after gastric resection for ulcer. *Wisconsin M. J.*, 44: 878, 1945.

[9] Levin, E., Kirsner, J. B., Palmer, W. L. and Butler, C. A comparison of the fasting nocturnal gastric secretions in patients with duodenal ulcer and in normal individuals. *Gastroenterology*, 10: 952, 1948.

[10] Levin, E., Kirsner, J. B., Palmer, W. L. and Butler, C. The fasting nocturnal gastric secretions in normal individuals and in patients with duodenal ulcer, gastric ulcer, and gastric carcinoma. *Arch. Surg.*, (in press).

[11] Kirsner, J. B., Levin, E. and Palmer, W. L. Observations on the excessive nocturnal gastric secretion in patients with peptic ulcer. *Gastroenterology*, (in press).

[12] Dragstedt, L. R. and Owens, F. M., Jr. Supradiaphragmatic section of the vagus nerves in treatment of duodenal ulcer. *Proc. Soc. Exper. Med. & Biol.*, 53: 152, 1943.

[13] Sippy, B. W. Gastric and duodenal ulcer: medical cure by an efficient removal of gastric juice corrosion. *J. A. M. A.*, 64: 1625, 1915.

that this is the attacking force responsible for the production of the lesion, the stimulus for pain and the cause of failure to heal. The digestive action of the gastric juice depends upon hydrochloric acid and pepsin; it is absent in achlorhydria. The most effective means of controlling the digestive attack is by controlling the free acidity. We have not yet found a satisfactory method of control; therein lies the ulcer problem. Intractability would indeed be a myth if complete control could be achieved.

WALTER LINCOLN PALMER, M.D.

Clinical Studies

Lysozyme Activity in Ulcerative Alimentary Disease*

1. Lysozyme in Peptic Ulcer

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FLEMING[1] gave the name lysozyme to a bacteriolytic agent present in nasal secretions, saliva, tears and egg-white. He hoped to prove it an effective antibiotic; however, lysozyme was subsequently shown to be active against saprophytes such as sarcinae, micrococci and megatherium while most pathogens were not attacked.[2]

The chemical nature of egg-white lysozyme was found to be that of a basic protein of low molecular weight requiring a sulfhydryl group for its activity.[3] Crystalline egg-white lysozyme was shown to have a molecular weight of about 18,000 and an isoelectric point of about 11,[4] i.e., it is the most basic protein found thus far in warm-blooded animals. The chemical nature of other lysozymes is less well known. Recently lysozymes of acidic nature were shown in the latex of certain Ficus plants[5] as well as in the latex of Hevea braziliensis, in both of which the concentrations are five to twelve times that in egg-white.

Lysis of susceptible organisms by lysozyme was found to be due to the hydrolysis of a mucoid component of the cell wall.[6] Recently this component was obtained as a high polymer mucopolysaccharide which was depolymerized and hydrolyzed at a rate comparable to the speed of bacterial lysis.[7] The fall in the viscosity of solutions of this material made possible an accurate viscosimetric assay of the enzyme. One unit of lysozyme was defined as the quantity which at 37°C. and pH 5.3 reduced the viscosity of a 0.4 per cent solution of the substrate to one-half in ten minutes.

A survey of the concentrations of lysozyme in man revealed the following concentrations: (1) Tears, 800 to 2,000 u/cc.; (2) serum, 0.5 to 1.5 u/cc.; (3) saliva, 1.3 to 2.0 u/cc. and (4) cartilage, 10 to 40 u/Gm. Tear glands of laboratory and some slaughter house animals, however, showed only about 1 unit/Gm. of gland. Samples of lyophilized or acetone-dried hog gastric mucosa revealed very high titers, ranging from about 800 to 2,000 units/Gm. This fact suggested an inquiry into the physiologic and pathologic rôle of lysozyme in the alimentary tract.

An etiologic rôle for lysozyme in alimentary ulcerative disease is suggested by: (1) Distribution of lysozyme along the digestive tract. (2) Increased concentration found in alimentary ulcerative disease. (3) Removal of surface mucus by the enzyme. (4) Production of ulcerative lesions by oral administration of crystalline lysozyme.

EXPERIMENTAL

Lysozyme was assayed viscosimetrically. The substrate was prepared from Micrococcus lysodeikticus. Each batch of sub-

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strate was tested for the amount of reducing sugars liberated in two and twenty hours on incubation with crystalline egg-white lysozyme.[7]

Gastric Mucosa. Either the fresh or dried mucosa* was extracted in a porcelain mortar with quartz sand or in a tissue grinder with ten times its weight of .1N HCl and centrifuged. Normal saline or buffer solutions extracted lower enzyme concentrations. For each extract the proper dilution was determined roughly and a duplicate run made in the proper dilution.

Resected human stomachs were obtained shortly after operation and samples of mucosa dissected from the submucosa. Inevitably some fibrous tissue accompanied the mucosa. The surface mucus was not disturbed by washing.

The average lysozyme concentrations of the mucosa of different histologic areas of six ulcerous stomachs and duodenums were as follows (in units per Gm. of wet weight): fundus, 16; antrum, 315; pylorus, 122; duodenum, 265. One carcinomatous stomach showed the following values in samples from uninvolved areas: fundus, 18; antrum, 35; pylorus, 120; duodenum, 200.

An attempt was then made to compare more fully the lysozyme content of different areas of ulcerous and carcinomatous stomachs. Figure 1 shows the approximate areas from which the samples were obtained.

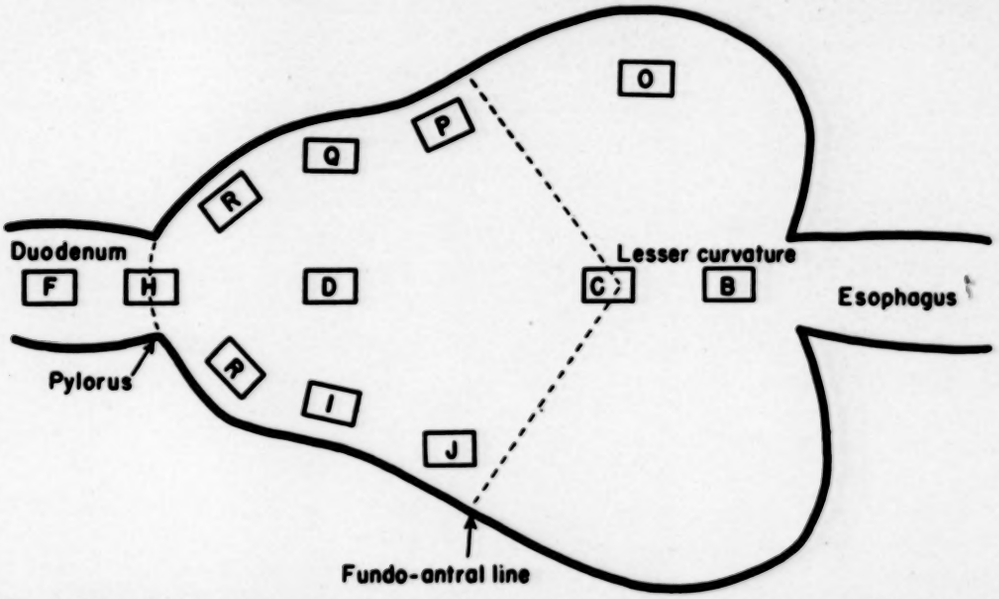

FIG. 1. Diagrammatic representation of a stomach opened along the greater curvature. The lettered blocks indicate the areas assayed.

Table 1 shows that the highest concentrations of lysozyme occur in the duodenum and pyloric regions where peptic ulcers occur most frequently. Any conclusions regarding the comparative values in carcinomatous and ulceratous stomachs must be highly tentative because of the small number of samples. On the basis of these results, however, there would appear to be no difference in the pyloric and duodenal regions. Factors which may have contributed to the scatter of these values are the difficulty in being certain that sections P, C and J were from the antrum rather than the fundus and the variable time elapsing between resection and assay.

Gastric Juice. Gastric juice was obtained by Levine tube aspiration, usually three hours postprandially. A few samples were procured after histamine, alcohol and Ewald meal stimulation. No significant changes in the lysozyme titers under these

* Generously prepared and furnished by the Sharp and Dohme Co. of Glenolden, Pa., and the Armour Laboratories, Chicago, Ill.

various conditions were noted even in the same individual.

Table II summarizes all data in thirty normal subjects, twenty-nine unoperated ulcer cases, six postoperative gastrectomies for ulcer patients, one chronic atrophic gastritis patient, two gastroduodenitis cases, five vagectomized individuals before and after operation, one assay on a patient following vagectomy and gastroenterostomy and three patients with marginal ulcers.

TABLE I
COMPARISON OF MUCOSAL ASSAYS IN ULCEROUS AND CARCINOMATOUS STOMACHS

Section	Ulcerous		Carcinomatous	
	Values	Mean	Values	Mean
C	2, 80, 50, 154, 13*, 13, 40, 115, 4	*57.2*	45	
D	388*, 526, 224, 84, 98, 185, 160*	*238*	121, 75, 169, 51	*104*
J	18, 16, 421, 50*	*126*	123, 428, 44	*198*
I	296, 140*, 204, 191	*208* } 155	26, 87, 114, 67	*74* } 94
Q	63, 154, 111*, 154, 130, 141, 124	*125* }	270, 37, 55, 93	*114* }
R	130, 298, 208, 156*	*198*	143	
P	41, 31*, 30, 100, 7	*42*	28, 37	*32*
F	800, 94, 272, 352, 417*, 570*, 190, 322	*376*	600, 362, 397, 286, 286, 299	*380*
H	575*, 77, 267, 157, 329, 244, 317, 101*	*258*	240, 260, 274	*258*
K	16			
B	13*, 64†	*39*		
O	16			

* From stomach with gastric rather than duodenal ulcer.

† From the region immediately adjacent to fundal ulcer.

Figure 2 shows the frequency distribution curves of the lysozyme titers of the gastric juice of the thirty normal individuals and twenty-nine unoperated ulcer patients. Both are markedly skewed curves, but the ulcer curve has a mode of five in contrast to one of two for the normal group. In the normal series there is only one titer above 25 units/cc., whereas there are six ulcer patients with titers greater than 25. The mean titer of the normal group was 7.69 units/cc. while the ulcer group averaged 14.30. Statistical analysis of these groups revealed a possibly significant difference of the means.

Inspection of Table II reveals that all seven frankly obstructed cases (as judged by intractable vomiting) had very low lysozyme titers, ranging from 0.2 to 4.5 units/cc. with a mean of 1.77. The mean of the unoperated ulcer cases minus those with frank obstruction is 18.3 units/cc.

These low lysozyme titers in obstructed cases may be due to two factors: one, the greater dilution of the enzyme with gastric retention and two, the destruction of lysozyme by pepsin. We have no data on the dilution factor but the inactivation by pepsin was studied *in vitro*. Two types of experiments were performed: in the first experiment dried hog gastric mucosa was extracted with .1N HCl and, after centrifugation, the supernate was assayed for lysozyme before and after incubation at 37°C. A control experiment was stored for the same length of time at 4°C. and then assayed. Table III illustrates the result.

The control left for two hours at 0°C. showed exactly 714 units/Gm.

In the second experiment 50 gamma of crystalline egg-white* lysozyme was incubated with 100 gamma of crystalline pepsin containing about 50 per cent magnesium sulfate in citrate buffer of pH 2.0. The controls and incubated mixture were diluted with .9 per cent NaCl at the specified time intervals and assayed for lysozyme activity. Table IV gives the results.

In a similar experiment, substituting 100 gamma of crystalline trypsin for the pepsin

* A portion of the crystalline egg-white lysozyme was prepared in this institution. For the remainder we are indebted to the Schering Corp., Bloomfield, N. J., and to the Armour Co., Chicago, Ill. The biologic activity of these samples was identical.

TABLE II

SUMMARY OF INFORMATION ON PATIENTS HAVING GASTRIC JUICE LYSOZYME ASSAYS

Name	Sex	Age	Clinical Status	Acid Level	Test Employed	Lysozyme Titer (Units/cc.)
Normal Subjects						
W. T.	♂	35	Occasional epigastric pains; no lesion demonstrable by x-ray	104/108	Ewald	5.8
A. M.	♂	61	No complaints except for osteoarthritis	3/6	Histamine	33
H. J.	♀	42	No complaints; acne rosacea	54/58	Ewald	7.5
C. D.	♀	34	Occasional epigastric pains; no lesion demonstrable	48/54	Ewald	1.5
W. V.	♂	26	Postprandial epigastric pain; deformed duodenal bulb by x-ray; no crater	84/88	Histamine	3.6
E. C.	♂	63	Occasional epigastric pains; negative gastrointestinal series	60/64	?	1.5
T. N.	♀	41	Right upper quadrant pain; film showed diverticula of hepatic flexure; negative gastrointestinal series	54/72	Ewald	5.7
A. P.	♂	60	No complaints	30/36	Histamine	20
M. P.	♀	50	No complaints	18/22	Histamine	16.5
C. D.	♀	35	"Gas pains"; no lesion demonstrable	70/78	Ewald	2.5
J. K.	♂	29	Check-up after known ulcer; "quiescent duodenal ulcer" on gastrointestinal series	22/26	Ewald	4.8
E. W.	♀	65	"Gas on stomach"; cholelithiasis; no gastrointestinal lesion	7/28	Histamine	16.1
J. P.	♂	27	No complaints	100/108	Histamine	1.82
					3 hr. postprandially	3.32 } 2.45 average
						2.2
A. N.	♀	23	No complaints			0.4
V. L.	♂	28	No complaints			1.9
K. M.	♂	47	No complaints	50/52	3 hr. postprandially	2
I. G.	♂	25	No complaints	128/132	Histamine	0.3
				48/52	3 hr. postprandially	2 } 5.35 average
						10
						9.1
J. G.	♂	29	No complaints	78/84	Histamine	1.25
J. H.	♂	43	Occasional dyspepsia	18/22	3 hr. postprandially	20 } 20.7 average
						21.4
S. S.	♀	18	No complaints	50/58	Histamine	.294
F. T.	♂	28	No complaints	78/84	Histamine	.667
D. O.	♂	26	No complaints	60/64	3 hr. postprandially	8.7 } 8.7 average
						8.7
K. H.	♂	27	No complaints	54/58	Histamine	10.3
T. B.	♂	28	No complaints	140/146	Histamine	2.8
D. L.	♂	31	No complaints	0/18	Histamine	16.7
M. M.	♀	29	No complaints	120/122	Histamine	0.17
C. M.	♀	?	No gastrointestinal lesion; other complaints not known			9.1
A. M.	♂	64	No gastrointestinal complaints; peripheral neuritis; senile arteriosclerosis	84/88	Ewald	4.76
C. L.	♀	49	Gas and burning pain in left upper quadrant and over precordium for six years; greatly enlarged heart by x-ray; myocardial damage on EKG; barium enema and gastrointestinal series negative	8/32	Ewald	15.6
J. M.	♂	?	No gastrointestinal complaints	54/58	Ewald	8.8
Unoperated Ulcers						
H. J.	♂	80	Postprandial epigastric pain; antral gastritis and duodenal ulcer	86/88	Ewald	17.6
E. T.	♂	48	Bleeding duodenal ulcer diagnosed on admission; pathologic report later showed duodenal ulcer, multiple superficial gastric ulcers and lymphosarcoma of stomach	10/14	3 hr. postprandially	40

TABLE II (*Continued*)

Unoperated Ulcers

Name	Sex	Age	Clinical Status	Acid Level	Test Employed	Lysozyme Titer (Units/cc.)
K. H.	♂	?	Admitted with hematemesis, melena; operation showed obstructing pyloric ulcer and multiple superficial gastric ulcers	79/87	Histamine	0.3*
J. W.	♂	30	Ulcer pain for 5 years; frequent tarry stools; vagotomy; duodenal ulcer	60/64	3 hr. post-prandially	24
A. S.	♀	71	Typical ulcer pain with prepyloric lesion; pathologic condition diagnosed carcinoma plus multiple ulcers of stomach	40/46	3 hr. post-prandially	20.7
A. L.	♀	35	Ulcer pain pattern for 2½ years; gastrointestinal series showed ulcer in duodenal bulb	38/44	3 hr. post-prandially	9.75
B. B.	♂	45	Melena and postprandial pain 4 months before admission; gastrointestinal series showed duodenal ulcer	110/120	3 hr. post-prandially	2
J. M.	♂	57	Duodenal ulcer discovered in work-up for obscure retrosternal pain	0/2	Fasting	10.4
F. G.	♂	52	Ulcer pain, hematemesis and melena; duodenal ulcer on gastrointestinal series; vagotomy	24/30	Fasting	60
J. S.	♂	63	Epigastric pain for 3 years; ulcer in duodenal bulb repeatedly demonstrated	104/112	3 hr. post-prandially	3.6 7.0 } 5.3 average
J. D.	♂	44	Vomiting for 4 months with postprandial epigastric pain for 6 months; gastrointestinal series showed duodenal ulcer	0/2	3 hr. post-prandially	7.5
C. D.	♂	46	6 months of epigastric pain; melena for 4 days preceding admission; gastrointestinal series showed spastic bulb and suggested a crater	86/96	3 hr. post-prandially	3.3
H. K.	♀	49	Melena and ulcer pain for 2 weeks before admission; gastrointestinal series showed spastic bulb and suggestive crater	36/40	3 hr. post-prandially	42.2
L. A.	♂	68	Ulcer pain for 4 years; duodenal ulcer seen on gastrointestinal series	83/94	3 hr. post-prandially	11.3
N. Y.	♂	?	Admitted once a year for 3 years for obstruction pyloric ulcer; gastrointestinal series showed hyperperistalsis and obstruction plus ulcer	52/60	3 hr. post-prandially	1.1*
A. S.	♂	51	Left upper quadrant pain and vomiting for 5 years; hiatus hernia and duodenal ulcer repeatedly demonstrated; had repair of hernia and vagectomy	32/38	3 hr. post-prandially	12.4
W. S.	♂	70	Gradual onset of gnawing pain 4 years before admission; bleeding on admission; has had melena, hematemesis and duodenal ulcer	78/84	3 hr. post-prandially	10.9
M. B.	♀	55	Entered for thyroidectomy (non-toxic nodular); complained of gnawing ulcer-type pain; gastrointestinal series showed duodenal bulb spasticity "consistent with ulcer"	20/24	3 hr. post-prandially	18.9
F. F.	♂	41	"Some" epigastric pain for 4 years; vomited 4 months before admission for intractable vomiting; gastrointestinal series showed pyloric ulcer plus obstruction	92/98	3 hr. post-prandially	0.4*
C. S.	♂	46	Has ulcer pain pattern and duodenal ulcer by gastrointestinal series	38/44	3 hr. post-prandially	25.4
V. M.	♂	42	Sharp epigastric pain; has had melena and hematemesis; gastrointestinal series showed ulcer on lesser curvature	10/18	3 hr. post-prandially	50.0
T. O.	♂	48	Ulcer demonstrated 7 years previously; bland diet relieved it for 7 years; ulcer pain returned in past year; had signs of perforation on admission which closed off spontaneously; had been vomiting	100/108	3 hr. post-prandially	3.8*

TABLE II (*Continued*)

Name	Sex	Age	Clinical Status	Acid Level	Test Employed	Lysozyme Titer (Units/cc.)
Unoperated Ulcers						
N. A.	♂	45	Epigastric pain with nausea; has hiatus hernia plus ulcer	62/74	3 hr. post-prandially	16.2
W. H.	♂	82	All complications of ulcer for over 8 years and is now vomiting	66/74	3 hr. post-prandially	0.2*
E. W.	♀	50	Characteristic ulcer pain; duodenal ulcer was repeatedly demonstrated	32/40	3 hr. post-prandially	5
F. P.	♂	61	Vague epigastric pains for 3 years and is now vomiting 6 times a day	100/109	Histamine	4.5*
H. W.	♂	51	Perforated duodenal ulcer in 1942; now vomiting and needs lavages	60/68	3 hr. post-prandially	2.1*
L. K.	♂	67	Has had a known ulcer for many years, and melena recently	120/130	3 hr. post-prandially	4.8
J. K.	♂	33	Chronic duodenal ulcer since the age of 19; now doing well on ambulatory diet; symptoms return upon indiscretion	22/26	Ewald	4.87
Marginal Ulcers						
C. L.	♂	59	Demonstrated bleeding ulcer at margin of Billroth II stoma; vagectomy	42/48	3 hr. post-prandially	62.9
D. R.	♂	55	Had Polya type gastric resection for duodenal ulcer five years ago; came in bleeding from marginal ulcer; vagectomy	0/4	3 hr. post-prandially	32.6
K. B.	♀	?	Gastroenterostomy 20 years previously; perforated marginal ulcer in November, 1946; refused vagectomy	96/98	3 hr. post-prandially	3.9
Repeat Runs on Patients Following Vagectomy						
N. A.	♂	45	Vagectomy for hematemesis and tarry stools from duodenal ulcer	0/4	3 hr. post-prandially	7.2 16.2 previous value 56% decrease
F. G.	♂	52	Classical ulcer history with melena and hematemesis; vagectomy performed	18/22	Fasting	50 60 previous value 16.7% decrease
J. W.	♂	30	Ulcer in duodenum for 5 years; gnawing pain and frequent melena; vagectomy performed	0/4	3 hr. post-prandially	10 24 previous value 58.4% decrease
D. R.	♂	55	Had Polya type gastric resection for duodenal ulcer 5 years ago; had bleeding marginal ulcer; vagectomy done	0/4	3 hr. post-prandially	27.2 32.6 previous value 16.6% decrease
C. L.	♂	59	Bleeding ulcer at margin of Billroth II stoma; vagectomy done	48/52	3 hr. post-prandially	16.2 62.9 previous value 74.4% decrease
Runs Following Gastrectomy (Hofmeister) for Duodenal Ulcer						
G. S.	♂	34	7 years of duodenal ulcer; gastrectomy; assay third postoperative day	0/28	3 hr. post-prandially	33.2
H. H.	♀	65	Multiple gastric ulcers; gastrectomy; recurrence of symptoms; no marginal ulcer seen on one gastrointestinal series	0/4	Histamine	61.6
J. L.	♀	63	Intractable ulcer pain for 30 years; gastrectomy; assay 17th postoperative day	50/56	3 hr. post-prandially	30.8
F. C.	♂	68	Intractable pain and vomiting; gastrectomy; assay 20th postoperative day	28/31	3 hr. post-prandially	46.2
C. C.	♂	63	15 years of duodenal ulcer; intractable vomiting; gastrectomy; assay 8th postoperative day	24/30	3 hr. post-prandially	15
S.	♂	?	Had burning pain following operation; exploration revealed gastric polyps	14/22	3 hr. post-prandially	22.6

TABLE II (*Continued*)

Name	Sex	Age	Clinical Status	Acid Level	Test Employed	Lysozyme Titer (Units/cc.)
Chronic Atrophic Gastritis Diagnosis by Gastrointestinal Series and Gastroscopy						
N. M.	♀	77	Has lost appetite with a weight loss of 40 pounds; no lesion discovered except thin gastric mucosa with shallow rugae	35/44	3 hr. post-prandially	5
Gastroduodenitis (Enlarged Rugae by Gastrointestinal Series)						
W. L.	♂	36	Mild epigastric pain at times; gastrointestinal series shows enlarged rugae	92/98	Histamine	22 47.6 35.1 average
S. C.	♂	39	Epigastric pains of crampy nature; little relationship to food; gastrointestinal series shows gastroduodenitis	76/80	Ewald	35.7 12.5
Assays after Gastroenterostomy for Obstruction						
J. B.	♂	66	Had pyloroduodenal ulcer with retention; gastroenterostomy done; assay 26th postoperative day	90/96	3 hr. post-prandially	16.2
H. T.	♀	64	Intractable vomiting; marked cicatrization of pylorus seen at gastroenterostomy; assay 7th postoperative day	28/34	3 hr. post-prandially	1.9
Runs after Subdiaphragmatic Vagectomy and Gastroenterostomy for Duodenal Ulcer						
H. J.	♂	43	Tarry stools, ulcer type pain; duodenal ulcer demonstrated; assay 9th postoperative day	36/42	3 hr. post-prandially	10.9

* Intractable vomiting.

at pH 7.0, there was no inactivation of lysozyme even after twenty-two hours. Because of this demonstrated inactivation of lysozyme by pepsin and because of the undoubted dilution of the enzyme by gastric retention, we have believed ourselves justified in omitting the seven frankly obstructed cases when comparing the mean of the ulcer group with that of the normal group. A statistical comparison of these

TABLE III

Time of Incubation in Hr.	Units of Lysozyme/Gm.	Per Cent Inactivation
0	714	0
1	445	38
2	164	77

TABLE IV

Time of Incubation in Hr.		Units per mg.	Per Cent Inactivation
4°C.	37°C.		
With Pepsin			
	0	869	0
	1	167	81
	2	74	92
	25	2.2	99.8
2		833	4.1
25		645	25.8
Without Pepsin			
	2	876	0
	25	690	20.6
25		800	7.9

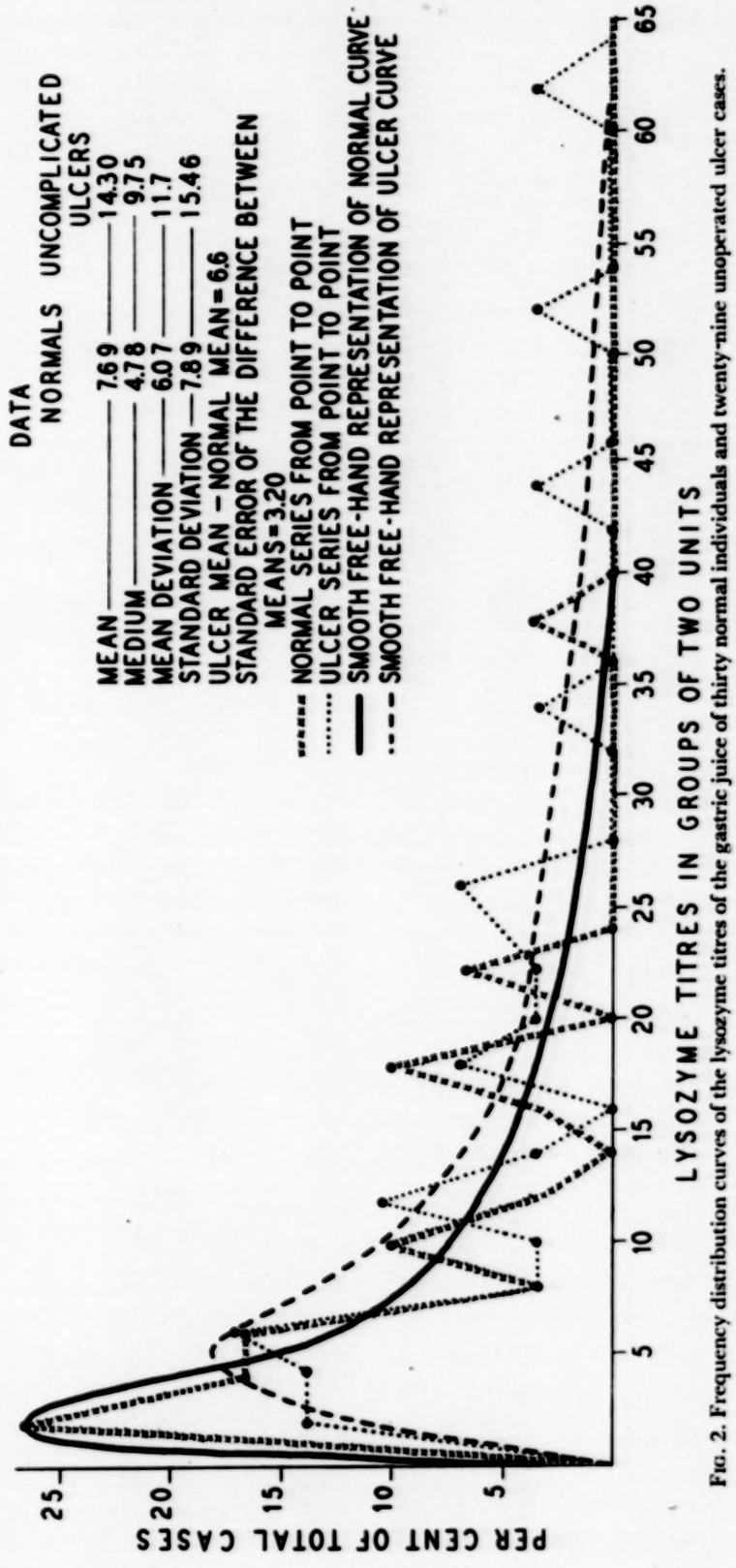

FIG. 2. Frequency distribution curves of the lysozyme titres of the gastric juice of thirty normal individuals and twenty-nine unoperated ulcer cases.

groups revealed a highly significant difference of the means.

Figure 3 illustrates various small groups of cases studied. The clinical data are summarized in Table II. The high titers in the postgastrectomy (for ulcer) cases and

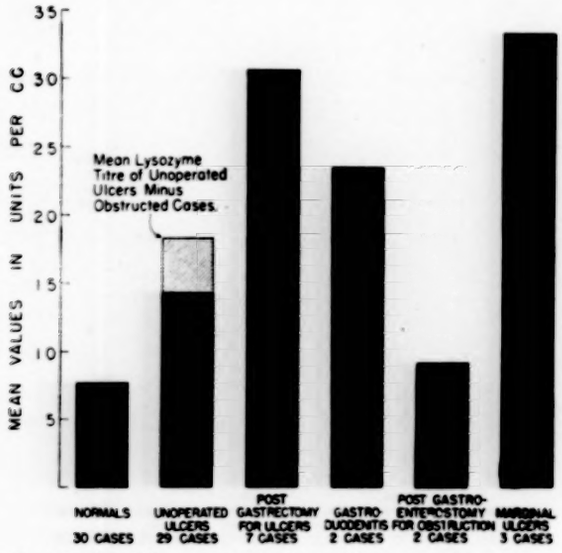

FIG. 3. Graphic representation of the mean lysozyme titres of all groups studied.

in the marginal ulcers seem significant since marginal ulcers frequently develop despite low or normal acid levels. (There was, in general, no correlation between lysozyme titers and acidity.)

Five individuals were studied before and after vagectomy. All the patients showed a decrease in lysozyme titer, ranging from 16.7 to 74.4 per cent with an average fall of 44.4 per cent. The possible connection between nervous tension and the lysozyme content of gastric juice is shown by the following observations: One individual with a negative gastrointestinal history showed on three occasions consistently elevated lysozyme titers (22, 47.6, 35.7) averaging 35.1 units/cc. The acid level was at the upper limit of normal (92/98 posthistamine). These levels were obtained while this young physician was preparing for his specialty board examinations. Because of slight epigastric pain a gastrointestinal series was done. This showed a definite antral gastritis with no evidence of ulceration. Following successful completion of the examination, the lysozyme level returned to 6.2 units/cc. with no change in the acid level. All symptoms disappeared. This single observation obviously requires further confirmation.

The gastric juices of three male patients with perforated duodenal ulcers were obtained before operation. In each case the volume was very high. The results were: (1) 2.4 units/cc., no free acid; (2) 23.1 units/cc., acidity 28/32; (3) 17.0 units/cc., acidity 40/44.

ACTION OF LYSOZYME IN THE CANINE ALIMENTARY TRACT

In order to investigate the effect of lysozyme on the mucosa of the dog the enzyme was administered to a dog with a Pavlov pouch and to dogs with intact alimentary tracts.

A Pavlov type pouch was constructed, consisting of a small amount of fundus, the antrum, the pylorus and a cuff of duodenum. It was then tacked to the skin by the duodenal cuff. After a suitable recovery period the dog was anesthetized. While supine, a solution of egg-white lysozyme in pooled human gastric juice was allowed to drip very slowly into the stoma of the pouch via a small glass intravenous needle adapter. During a four-hour period of anesthesia, lysozyme in a concentration of 7,500 units/cc. was allowed to drip from a low height into the pouch at the rate of approximately three drops per minute. All precautions possible were taken to avoid traumatizing the mucosa and to negate any possible mechanical factor in producing loss of mucus from the mucosa of the pouch. After approximately 350 cc. of this mixture had entered the pouch the latter was removed *in toto*. Following inspection, it was immediately fixed in Bouin's solution without cleansing, washing or rubbing. Gross examination of the pouch showed a remarkable "scrubbed" appearance of the mucosa. Very little mucus was to be found, an observation substantiated by microscopic examination. Representative sections were

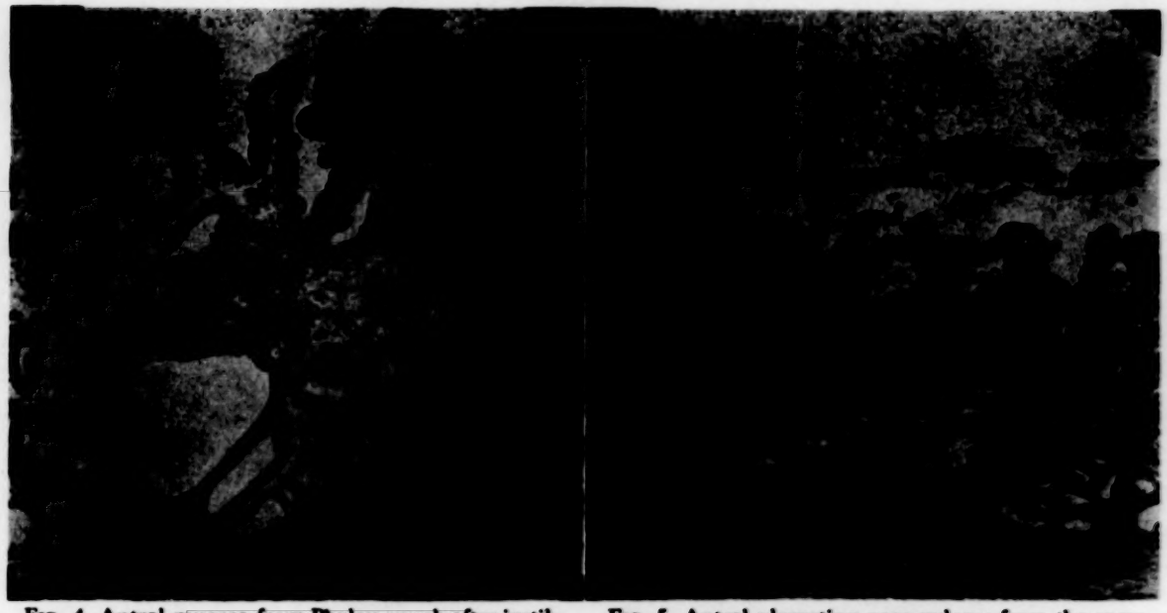

FIG. 4. Antral mucosa from Pavlov pouch after instillation of lysozyme in pooled human gastric juice. Note cystic dilation of gastric glands.

FIG. 5. Antral ulceration near pylorus from the same experiment illustrated in Figure 4.

taken of the pouch and study of the histologic preparations showed that the protective mucous coat found regularly on the mucosa of the normal stomach was completely lacking. The mucus contents of the gastric pits deep in the lamina propria disappeared, a condition which could not have been produced mechanically by a slowly flowing minute quantity of liquid on the surface of the mucosa.

Figure 4 shows complete absence of the surface mucus on the antral mucosa of the pouch used in this experiment. Also illustrated is the unusual cystic dilatation of the gastric glands deep in the lamina propria. The connective tissue of the lamina propria is edematous. It might be suspected that the cystic dilatation is due to an osmotic effect caused by the hydrolysis of a substrate in these glands.

Figure 5 illustrates a small antral ulceration near the pylorus produced in this experiment. The lesion is characterized by loss of the superficial epithelium extending well into the necks of the glands. Because of the depth of the destruction, this lesion could not have been produced by trauma.

For purposes of comparison and control the functioning stomach of the same dog (separate from the pouch) was removed at this time and treated with exactly the same technic. Histologic examination of this gastric mucosa discloses a much greater amount of mucus on the epithelial lining of the stomach. (Fig. 6.)

In another animal experiment lysozyme was allowed to drip slowly through a Levine tube at approximately three drops per minute into a normal functioning dog's stomach (under nembutal anesthesia) over an eight-hour period. In this case the lysozyme was given in a concentration of 3,200 units/cc. of normal saline. Physiologic saline was used in this experiment in order to determine whether the dissolution of the mucus in the previous experiment was due to the gastric juice or to lysozyme activity. At the end of eight hours the stomach was resected. It was then fixed by the same careful technic without cleansing or unnecessary handling. Blocks of tissue from typical areas of this organ show much the same histologic picture. A representative photomicrograph is shown in Figure 7. The deeper mucus apparently disappears first, leaving no support for the uppermost layer which then "peels" off as shown. It would appear from comparison of the specimens

FIG. 6. Normal canine gastric mucosa from a portion of the stomach not connected with the Pavlov pouch. Note the presence of surface mucus.

from each of the two stomachs that the disappearance of the mucus is due to lysozyme.

Three normal dogs were given crystalline egg-white lysozyme by mouth. The first dog was given 30,000 units twice a day in enteric-coated gelatin capsules (approximately 42 mg. per day) for thirty-eight days, or 2,280,000 units *in toto*. The second dog received 30,000 units in 20 cc. of cherry syrup twice a day for thirty-eight days. The third received 270,000 units twice a day for three and one-half days or a total of 1,890,000 units.

The dogs showed no noticeable systemic effects from their lysozyme administrations. The second dog weighed 9.6 Kg. at the start of the experiment and 11.6 Kg. at the end. The first lost 0.3 Kg. from an initial weight of 8.5 Kg., while the third weighed 5.6 Kg. initially and 5.7 Kg. after three and one-half days. The stools were characteristically (although not always) loose, "mucoid" and unformed in the dogs receiving lysozyme, while the remainder of the dogs in that animal room, receiving an identical diet, had formed stools. The average weight of stools per day of the three dogs and one control were as follows:

	Final Weight	Average Weight Stool
Control dog	10.2 Kg.	38.5 Gm./day
Dog No. 1	8.2 Kg.	94.5 Gm./day
Dog No. 2	11.6 Kg.	88.5 Gm./day
Dog No. 3	5.7 Kg.	80.0 Gm./day

Guaiac tests on the stools of dogs Nos. 1 and 2 on three spaced occasions were consistently negative. A guaiac on the stool of Dog No. 3 was negative after two days of lysozyme administration.

Stool lysozyme assays were done on one occasion for each dog. The first dog had a level of 15.4 units per Gm. of stool (wet weight) and the second dog a titer of 6.8 units per Gm. in the midst of lysozyme administration. The third dog had a level of 91 units per Gm. on the evening of the first day of administration. These are high stool titers in comparison with the level of .04 units/Gm. obtained in the stool of one normal dog. Assuming these titers to be the

7 8

FIG. 7. Effect of lysozyme in saline on the normal canine gastric mucosa when administered by a Levine tube.
FIG. 8. Superficial ulceration in the fundus of dog (1) receiving 30,000 units of lysozyme twice a day in enteric coated capsules. Note complete absence of superficial mucosa with disappearance of the mucous cells in the necks of the glands. The parietal cells are relatively unaffected.

average lysozyme content of the stool, dogs 1, 2 and 3 put forth 1,459, 602, and 7,280 units per day, respectively.

The specimens assayed lay in the cages for a variable amount of time not exceeding two hours before they were collected. Some decrease in the lysozyme content of the stools doubtless occurred in this interval; however, a much greater part of the loss from the amount administered must have occurred within the alimentary tract.

After the stated times the dogs were autopsied and the alimentary tracts removed *in toto*. The first dog's mucosa had a hyperemic, edematous appearance throughout the small intestine whereas the stomach and colon appeared essentially normal. However, there was an apparent lack of surface mucus in the antral and pyloric areas. Five definite superficial ulcerations were noted along the small intestine. One was present in the duodenum, two in the jejunum and two in the ileum. The largest (1 by 1.2 cm.) was 5 cm. beyond the pylorus.

The second dog had essentially the same general mucosal appearance. Three ulcerations were seen, the largest in the jejunum (1 by 1.9 cm.) with two in the ileum.

The third dog showed a superficial ulceration at the pylorus; otherwise, the stomach was grossly essentially normal. The small intestine and colon were fiery red, especially the terminal ileum. Superficial serpiginous ulcerations were noted throughout the small intestine, becoming more numerous distally. The colon showed similar lesions with hyperemia and edema.

Histologically, the lesions were characterized by loss of superficial epithelium and complete lack of superficial mucus. There was fragmentation of the lamina propria, of the valvulae conniventes, with edema and extreme hyperemia of the lamina propria. In the most marked lesions extensive lymphocytic and plasma cell infiltration was noted. The microscopic findings were most marked in the terminal ileum of the third dog where there was a resemblance to regional enteritis as seen in man. Figures 8, 9 and 10 illustrate the type of lesion produced in these feeding experiments. The histologic descriptions accompany the figures.

COMMENTS

Data have been presented indicating that lysozyme activity may be an etiologic factor in the pathogenesis of peptic ulcer.

FIG. 9. Pyloric ulceration in dog (3) receiving 270,000 units of lysozyme twice a day for three and one-half days in enteric coated capsules. Note the marked cystic dilation of a gastric gland.

FIG. 10. Deep ulceration of the terminal ileum of dog (3). The necrosis penetrates the entire thickness of the mucosa and is accompanied by an intense round cell infiltration.

The distribution of lysozyme in the various histologic areas of the stomach is consistent with this supposition. One of the unanswered problems in gastric pathology has always been the fact that peptic ulcers do not ordinarily arise in the area where pepsin and HCl are produced. According to our hypothesis, the rôle of pepsin and HCl in the pathogenesis of peptic ulcer may be secondary to the removal of the surface mucus by lysozyme. The high concentration of lysozyme in the ulcer-bearing areas is in accord with this hypothesis. This supposition, like its predecessors, does not explain the occurrence of single ulcers. One would have to postulate a highly localized overproduction of lysozyme in the ulcerating area, or additional unknown factors. Lysozyme titers of the gastric juice of ulcer patients show a statistically significant but not impressive increase over those of normal subjects (compared, for example, to the increased titers of the stools of chronic ulcerative colitis). It must be assumed that the lysozyme titer of the gastric juice inadequately represents the true enzymatic activity. The volume of the gastric fluid and destruction by pepsin are factors whose influence on the lysozyme titer has not been evaluated.

The substrate of lysozyme in the human alimentary tract has not been demonstrated with certainty. The known mucopolysaccharides of hog gastric mucosa,[8] i.e., the neutral and acid polysaccharides, are not depolymerized or hydrolyzed by lysozyme.* This was determined by viscosimetric and reductometric methods. Likewise, an enzyme mixture obtained from Clostridium welchii[9] which hydrolyzed the neutral polysaccharide fraction did not contain lysozyme. This lack of information concerning the substrate is an important missing link in the argument.

The action of lysozyme on the mucosa is best illustrated by the canine experiments. Removal of the surface mucus, localized ulcerations, and intense inflammatory reactions following lysozyme administration were all produced in these studies. The relative absence of gastric disturbances in the feeding experiment as compared with the first experiments mentioned probably emphasizes the importance of the time relationship. It can be assumed that the enzyme in the deeply anesthetized dog remained in the stomach in high concentration.

* This is not surprising since in their preparation the mucosa is allowed to autolyze and is further subjected to peptic and tryptic digestion.

Egg-white lysozyme, which was employed in the canine experiments, has a pH optimum of 5.3 with an effective activity from ~pH 3.9 to ~pH 7.0 while human gastric lysozyme has an optimum at pH 5.93 and an effective activity range from ~pH 4.6 to ~pH 7.1. The shape of the pH activity curves of the two lysozymes is, however, almost identical. On purification, hog gastric lysozyme (unlike that of Ficus) behaves toward adsorption on bentonite and toward elution by various solvents exactly as does egg-white lysozyme. It might be assumed that the low pH of the gastric juice was incompatible with lysozyme activity. However, the pH of the mucus in the gastric pits and in the deeper layers of the surface mucus can be assumed to be considerably higher than that in the lumen.

In conclusion, lysozyme, like pepsin and hydrochloric acid, is a probable etiologic agent in the pathogenesis of peptic ulcer. This does not preclude the possibility of additional factors.

SUMMARY

1. Lysozyme, a mucolytic enzyme, has been found in the gastric mucosa of animals and man in a relatively high concentration.

2. The enzyme is present in normal human gastric juice.

3. In man the mucosal concentration of lysozyme is very low in the fundus and increases to a maximum in the first portion of the duodenum.

4. The mean lysozyme titer of the gastric juice of ulcer patients is increased over that of normal individuals.

5. Frankly obstructed ulcer cases showed a uniformly low lysozyme titer, due either to dilution or destruction of lysozyme by pepsin. This destruction was demonstrated *in vitro*.

6. Five ulcer subjects studied before and after vagectomy showed a mean fall in lysozyme titer of 44 per cent.

7. In one Pavloc pouch dog a superficial antral ulceration and complete removal of the surface mucus of the pouch was produced in four hours by the instillation of crystalline egg-white lysozyme in pooled human gastric juice.

8. Upon instillation of egg-white lysozyme in saline into the intact stomach of a dog for eight hours complete removal of the surface mucus without ulceration was produced.

9. In three normal dogs oral administration of lysozyme in enteric-coated capsules or in cherry syrup produced a pyloric, antral and fundal ulceration in one dog and a fundal lesion in another. All dogs showed multiple ulcerations, hyperemia and edema of the entire small intestine. In addition, one dog showed ulceration, hyperemia and edema of the colon.

10. The probable etiologic rôle of lysozyme in peptic ulcer is discussed.

Acknowledgments: We are deeply indebted to Dr. Arthur P. Stout for his encouragement and advice during this study, particularly in the interpretation of the histologic data; and we wish to acknowledge the generous support of Dr. John S. Lockwood throughout this investigation, the aid of Dr. John W. Fertig in the statistical analysis of the assay results, and the technical assistance of Miss Janice Super.

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Lysozyme Activity in Ulcerative Alimentary Disease*

II. Lysozyme Activity in Chronic Ulcerative Colitis

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A STUDY of lysozyme activity in chronic ulcerative colitis was suggested by the superficial resemblance between this disease and peptic ulcer. The presence of lysozyme in stool seems to have been established only in breast fed infants while the stools of infants fed artificially have been reported to be free of the enzyme.[1] (The tests employed were not sufficiently sensitive to detect small concentrations of the enzyme.) These findings have been confirmed by various authors[2] and correlated with high lysozyme titers in human milk and its absence in cow's milk. These data have been confirmed by viscosimetric measurements.[3]

In the present study the stools of patients with chronic ulcerative colitis were found to contain a great deal more lysozyme than those of normal individuals. Concomitant with clinical improvement the lysozyme titer falls. These facts and the experimental production of ulcerations in the small and large intestine of the dog by oral lysozyme administration, as reported in the preceding paper, suggest that lysozyme may be the chemical agent initiating the local lesions of ulcerative colitis.

EXPERIMENTAL

Stool specimens were collected† and kept frozen until ready for assay. Control experiments showed no decrease in lysozyme titer when stool specimens were kept in this manner for as long as one month. Samples of well mixed stools were weighed on an analytic balance and mixed with ten times their weight of .1N HCl. This mixture was then triturated in a mortar or tissue grinder and centrifuged. The clear supernate was then assayed viscosimetrically as described in our previous paper. When possible, a twenty-four-hour stool specimen was collected in order to determine the total twenty-four-hour output of lysozyme. The mucosal assays were handled in the same fashion as described in the preceding paper.

Table 1 summarizes the assays of individual stools for various groups of patients. This table shows a 27-fold increase in the mean titer of the chronic ulcerative colitis stools over that of the normals, and a 46-fold increase over that of the stools of normal individuals following purging. High enzyme titers were found in the surface mucus. (This material is a mixture of mucus and detritus.) In contrast to the very high titers in active C.U.C.* three stools of patients in remission (normal stool consistency, one to three bowel movements per day, absence of mucosal hyperemia and

† Some of these specimens from patients with chronic ulcerative colitis were obtained through the courtesy of Dr. Henry W. Cave and Dr. Z. T. Bercowitz of the Roosevelt Hospital and the New York Post-graduate Hospital, respectively.

* Chronic ulcerative colitis is hereinafter abbreviated to C.U.C.

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friability and healing ulcerations by sigmoidoscopy) showed rather low enzyme values.

Ileal stools from three patients whose C.U.C. had necessitated ileostomy had low enzyme titers, indicating that excessive lysozyme is produced in the colon rather than the ileum in C.U.C. Excessive mucus in the stool apparently is not a necessary corollary of a high lysozyme titer.

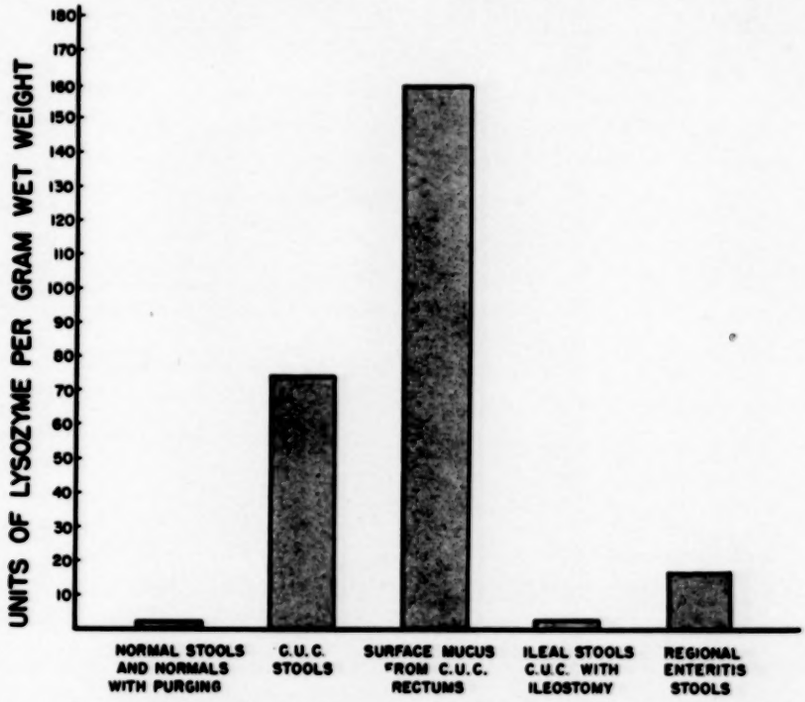

FIG. 1. A comparison of the mean lysozyme titres in four groups studied.

Table II shows the elevated mean lysozyme titers of the stools of six individuals with regional enteritis. There is a 6-fold increase in the mean titer over that of normal stools.

Figure 1 is a graphic representation of the data in Tables I and II.

In Table III the daily output of lysozyme in various groups is tabulated. There was a 6.7-fold increase in the mean output of normal individuals with purging over that of normal stools. However, there was a 168-fold increase in the lysozyme output in stools of patients with C.U.C. over normal outputs, and a 25-fold increase in C.U.C. over the daily output in purged normal subjects. One patient with acute regional enteritis also showed a high twenty-four-hour output. The 6.7-fold increase in the daily output in the purged normals merits some comment in view of the decrease in the units of enzyme per Gm. of stool in these individuals. (Table I.) This behavior contrasts sharply with stools of C.U.C. when both the units per Gm. and the twenty-four-hour output are markedly increased. It cannot be decided at present whether the increased daily output in purging is due to an increased production of lysozyme by the mucosa or to a decreased rate of enzyme inactivation due to a rapid expulsion of the feces.

One case of acute amebic colitis and one case of non-tropical sprue showed a lysozyme content of 38 and 4.6 units per Gm. of stool, respectively. These conditions will be studied further. In a few patients with C.U.C. in whom lysozyme was assayed in the gastric juice the titers were within the normal range. Free acid was absent in two of the four patients. Tears and serum likewise showed normal lysozyme titers.

Intestinal lysozyme seems to be locally produced by the mucosa. This is suggested

by the data in Table IV. This table shows the lysozyme titers of the mucosa of various portions of the intestine. Four acute C.U.C. patients had a mean mucosal lysozyme content 8.5 times greater than that of normal colon mucosa. In quiescence pro-

TABLE I

Source	Individual Titers (Units/Gm. Wet Weight)*			Mean Titer
Normal stools (6 cases)	.5	9.4	4.4	2.7
	.2	.8	.9	
Normal stools (after purging with $MgSO_4$ and castor oil) (8 cases)	.4	3.9	1.0	1.6
	.8	1.3	.1	
	1.6	3.8		
Chronic ulcerative colitis stools (32 cases)	28.3	48.7	22.3	73.6
	49.0	10.5	180.9	
	33.3	47.0	103.7	
	24.2	119.4	4.1	
	35.0	25.0	46.0	
	49.8	125.0	125.0	
	84.0	20.0	160.0	
	86.5	18.5	9.8	
	109.6	22.3	87.0	
	78.2	40.0	39.2	
	21.8	502.0		
Surface mucus from rectosigmoids of chronic ulcerative colitis patients (6 cases)	43.5	80.0	15.7	158.1
	167.0	466.0	176.5	
Chronic ulcerative colitis stools, clinically in remission (3 cases)	10.8	1.0	17.1	9.6
Ileal stools from individuals with C.U.C. (3 cases)	.1	2.0	3.6	2.8
Stools from patients with carcinoma of rectum; much mucus (2 cases)	.9	2.7		1.8
Idiopathic diarrheas with much mucus (3 cases)	.1	1.0	5.0	2.1

* Each individual titer represents the lysozyme content of a stool specimen from a different person.

duced by surgical diversion of the fecal stream the lysozyme content of the mucosa fell to essentially normal levels. Normal ileum showed the same enzyme content as the normal colon. One patient with regional enteritis had a markedly elevated lysozyme content (33 units) in the grossly involved portion of the ileum. A specimen from the ileum proximal to the area of gross involvement showed a slightly elevated titer. One-fourth of the ascending colon in this case was ulcerated. The lysozyme titer, however, was normal. It may be suggested that the elevated lysozyme of the ileal stool was re-

TABLE II

Source	Individual Titers (Units/Gm. of Wet Weight)			Mean Titer
Regional enteritis (6 cases)	30	7.0	.2*	16.5
	12.2	42.6	6.9	

* Three years postileocolectomy; persistent "watery" diarrhea, no blood or excessive mucus.

TABLE III

Source	Individual Outputs 24 Hours (Units)				Mean Output (Units)
Normal stools	39	528	27.5	39.5	158
Normal stools after purging	647	18.3	1940	380	1064
	879	582	3000		
Chronic ulcerative colitis stools	44,000	328*	64,500	4720	26,568
	22,563	2080	39,200	1950	
	59,024				
Regional enteritis	16,750				

* In "healing phase" clinically.

sponsible for this. Following ileocolectomy, this patient's stool lysozyme content fell from 30 to .5 units/Gm. The slightly elevated values found in the mucosa of the ileum proximal to regional enteritis and to retrograde involvement of the ileum by C.U.C. may emphasize the similarity of the two diseases.

Circumstantial evidence that lysozyme plays a significant rôle in the pathogenesis of C.U.C. is provided by a limited number of serial stool enzyme determinations in patients during an exacerbation of their disease and during remission. Concomitant with clinical improvement there was a fall in the lysozyme titer in the stool. In Figures 2 and 3 the results of lysozyme studies are summarized in patients who improved or failed to improve on specific therapy. These

patients received retention enemas of a 10 per cent suspension of 2-(*p*-nitrobenzene sulfonamido)thiazole (nisulfazole) in pectin.* Successful treatment of C.U.C. with this drug has been reported by Major.[4] In our experience in the therapy of twenty-one patients with C.U.C. with nisulfazole there was coincident symptomatic improvement in thirteen, no improvement or a progression of symptoms in six and equivocal response in two. The patients have been followed for intervals of four to fourteen months. Improvement was characterized by decrease in the number of daily bowel movements, disappearance of blood in the stools, improved appetite and weight gain occurring within two weeks after onset of therapy. At this time sigmoidoscopic examinations usually did not reveal impressive regression of the mucosal lesions; however, when remission was maintained there was healing of ulcerations, decrease of edema and lessened friability of the mucosa. Although three of the patients have had sustained remissions following a single course of nisulfazole (one patient is asymptomatic eleven months after therapy), in the other cases it has been necessary to

TABLE IV

	Type of Mucosa	Individual Lysozyme Titers				Mean Titer	Remarks
1.	Normal colon	4.1 3.3	3.5 3.0	3.0 10.0	8.0	5.0	Specimens from uninvolved areas of colons resected for carcinoma
2.	Biopsies from rectosigmoids of acute C.U.C. patients	42	40	54	34	42.5	All of these cases had an acute exacerbation at time of biopsy; rectal involvement proven sigmoidoscopically
3.	Mucosa from resected colons in quiescent state following ileostomy or colostomy more than 6 mo. previously	10 11 4	5 4	6 5	8 3	6.2	Although these colons were extremely fibrotic necessitating resection; there was no rectal discharge or other evidence of activity at time of resection
4.	Normal ileum	6.4	5.4	3.5	....	5.1	From ileums resected for malignancy
5.	Ileum with regional enteritis	33.0*	....	....	....	....	This patient had ileocolectomy for regional enteritis; there were ulcers in ascending colon also
6.	Ileum proximal to regional enteritis	18.0	13*	....	....	15.5	From item No. 5 and another where side-tracking ileocolostomy was done
7.	Ulcerated colon in regional enteritis	.....	5.4*	....	....	....	Specimen was from near an ulceration
8.	Ileum proximal to "retrograde involvement by C.U.C."	.....	12	....	....	....	The ileum had the chara eristics of regional enteritis ct
9.	Normal appearing ileum with entire colon involved by C.U.C.	.....	3.5				

* Specimens from the same patient with regional enteritis.

* Generously supplied by George A. Breon and Company, Kansas City, Mo.

continue small daily retention enemas of the drug in order to control symptoms. No significant toxic manifestations have been encountered. As can be seen in the figures there was a decrease in the lysozyme excretion in the patients who showed clinical improvement whereas the titer remained high when the patients' condition was not altered. Since C.U.C. is characterized by spontaneous remissions and its course can be significantly altered by psychotherapy, we hesitate at this time to ascribe the improvement noted in our patients to nisulfazole. However, the results have been sufficiently encouraging to warrant further clinical trial.

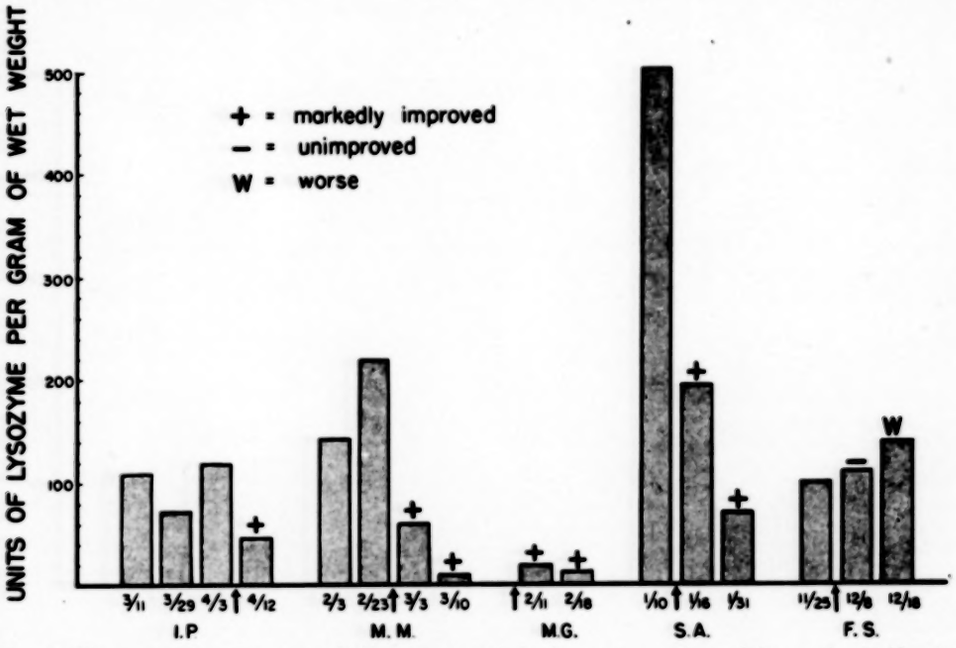

FIG. 2. The correlation between clinical status and the lysozyme content of the stool; nisulfazole therapy begun in the intervals indicated by arrows.

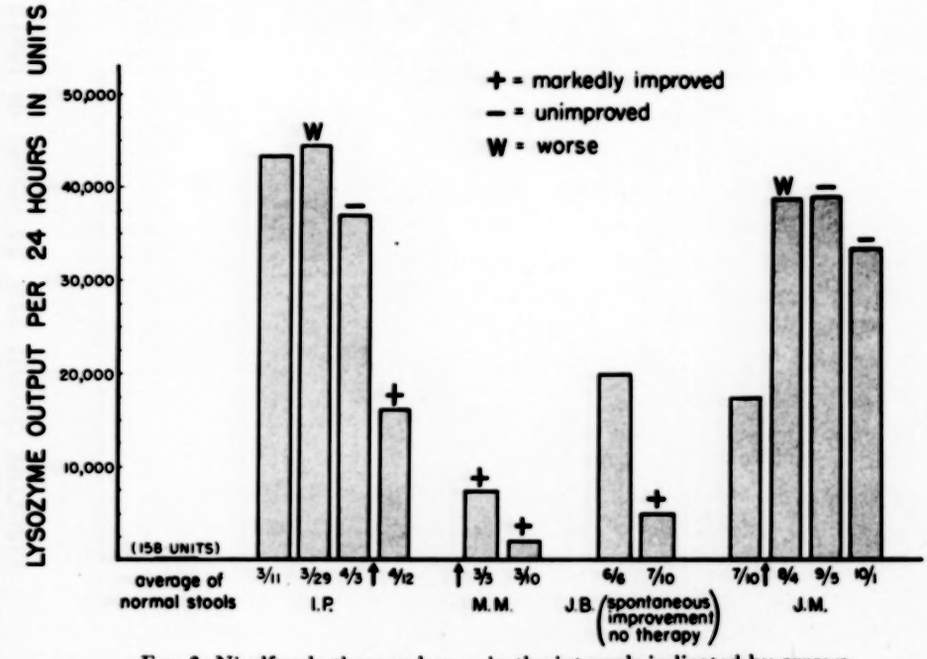

FIG. 3. Nisulfazole therapy begun in the intervals indicated by arrows.

The apparent efficacy of nisulfazole in the treatment of some cases of C.U.C. prompted an investigation into a possible inhibitory effect of this drug on lysozyme activity. Nisulfazole, as well as other compounds, inhibited lysozyme *in vitro* to varying degrees. This inhibition varied to a considerable extent with the source of the lysozyme and with the purity of the substrate.

Crystalline egg-white lysozyme in a concentration of 2 gamma/cc. was mixed with an equal volume of the inhibitor dissolved in saline. One cc. of the mixture was then added to 5 cc. of the substrate and the lysozyme assayed. The same dilution of lysozyme in saline served as a control.

Nisulfazole could only be tested in a concentration of 20 mg. per cent (.0007 M), its limit of solubility. The following inhibitions (in per cent) were found with nisulfazole and with equimolar concentrations of some related compounds: (1) Sulfathiazole, 25 per cent; (2) NH_4-*p*-nitro-benzene-sulfonate, 15 per cent and (3) Nisulfazole, 42 per cent.

The multiplicity of factors involved in enzyme inhibition experiments renders interpretation difficult and at present the mechanism of this inhibition is unknown.

Use of anionic detergents as inhibitory agents was suggested by the basic nature of egg-white and mammalian lysozyme. A detailed report on these compounds will be published later. The most effective inhibitors were the normal alkyl sulfates of the series C_{10} to C_{18}.* The maximum inhibition seems to be reached with the C_{16} compound. For example, in the same experiment just tabulated, Na dodecyl sulfate gave 64 per cent inhibition while hexadecyl and octadecyl sulfate in .0001 M concentration showed 85 per cent inhibition.

The lysozyme activity of human gastric juice, of extracts of human and hog gastric mucosa, of human tears and of normal human stools were inhibited to a similar degree by the alkyl sulfates. Extracts of C.U.C. stools, however, were not inactivated by nisulfazole or alkyl sulfates at these concentrations. They were inhibited when the concentration of alkyl sulfates was increased 10-fold.

The reason for this discrepancy seems to be the presence of proteins in the C.U.C. stools which compete with lysozyme for the inhibitors. Thus, a 1:20 dilution of serum completely prevented the inactivation of egg-white lysozyme by .0001 M hexadecyl sulfate. The source of this increase in protein can be considered to be the serous exudate from the colonic ulcers.

* We thank E. I. duPont Co. for the generous gift of these compounds.

COMMENT

The postulated etiologic rôle of infection in the pathogenesis of C.U.C. has fallen into disrepute because of repeated failures to demonstrate a characteristic bacterial flora in the disease. The almost uniformly high lysozyme content of the stools and mucosa, the fall in the enzyme titers with clinical improvement and the experimental production of ulcerations by administration of lysozyme to dogs all point strongly to lysozyme as an etiologic agent in chronic ulcerative colitis.

As in peptic ulcer we assume two stages in the pathogenesis of this disease: First, removal of the surface mucus with dissolution of the mucous cells and second, necrosis of the denuded tissue by proteolytic enzymes, presumably furnished by microorganisms. Similar findings in a limited number of cases of regional enteritis suggest that this also is a high lysozyme disease. The reason for localized overproduction of the enzyme in these diseases is obscure.

SUMMARY

1. The stools of C.U.C. patients have a mean lysozyme content 27 times that of normal stools.

2. The mean twenty-four-hour output of lysozyme in C.U.C. stools is 168 times that of normal stools.

3. Upon purging the twenty-four-hour output of lysozyme in normal individuals is

6.7 times that of normal stools while the concentration of the enzyme decreases by about one-third.

4. The lysozyme content of regional enteritis stools is 6.1 times that of normals.

5. With clinical improvement, the lysozyme titers and daily outputs fall.

6. The colonic mucosa of individuals with acute C.U.C. shows an 8.5-fold increase in lysozyme content over that of normal colons.

7. These data, together with the experimental production by lysozyme of ulcerations in the canine alimentary tract, indicate that lysozyme is an etiologic agent which locally initiates the lesions of chronic ulcerative colitis.

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Bleeding Peptic Ulcer*

A Review of Fifty-seven Consecutive Cases

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THIS paper is a presentation of fifty-seven consecutive cases of bleeding from the upper gastrointestinal tract. This series was not chosen haphazardly but includes all cases of initial or repeated hemorrhage from peptic ulceration which came under our supervision. The diagnosis in each case was compatible with either gastric or duodenal ulcer as shown by x-ray and/or by the clinical, physical and laboratory findings. There were no deaths in our series.

TABLE I

FINAL DIAGNOSIS OF THE UPPER GASTROINTESTINAL TRACT LESION

Lesion	Male Patients	Female Patients
Gastric ulcer	13	5
Duodenal ulcer	28	10
Gastric and duodenal ulcers combined	1	

There were thirty-nine duodenal ulcers and nineteen gastric ulcers in our series, giving a ratio of 2.05 to 1. Duodenal ulcer is classically stated to occur from three to ten times more frequently than gastric ulcer. Thus it is seen that the location of the ulcer is not a factor in the occurrence of hemorrhage therefrom. The incidence of hemorrhage from peptic ulcer is stated to be between 10 and 30 per cent. Collins and Knowlton[1] have reported an incidence of 3.8 per cent in 2,620 cases of ulcer seen at the Cleveland Clinic.

Bleeding may take place at any age, but the majority of cases are stated to occur in the fourth and fifth decades of life. Tidmarsh[2] believes that the reasons for this latter age distribution lie in the fact that arteriosclerosis is present in the older patient and second, there is a prolonged duration of the disease with marked callus formation in the ulcer. Both conditions predispose to hemorrhage since they interfere with the natural factors which tend to arrest bleeding. Chaikin and Tannenbaum[3] have reported a series of 121 cases of bleeding peptic ulcer with the following age distribution: second decade, nineteen patients; third decade, forty-nine; fourth decade, twenty-seven; fifth decade, eighteen and sixth decade, eight. These authors believe that hemorrhage from peptic ulcer is a disease of the younger age group and quote Goldman and Crohn who also observed this.

TABLE II

HEMORRHAGE IN FEMALES IN OUR SERIES ACCORDING TO AGE DISTRIBUTION

Ages	First Hemorrhage		Second Hemorrhage	
	No. Patients	Per Cent	No. Patients	Per Cent
20–24	2	13.33	0	.....
25–29	2	13.33	0	.....
30–34	0	.....	1	14.28
35–39	0	.....	0	.....
40–44	2	13.33	1	14.28
45–49	2	13.33	3	42.85
50–54	1	6.66	1	14.28
55–59	2	13.33	0	.....
60–64	1	6.66	1	14.28
65–69	1	6.66	0	.....
70–74	2	13.33	0	.....
Total	15	.....	7	.....

One female patient in the age group 40–44 experienced six separate hemorrhages before coming under our treatment.

* From the Department of Internal Medicine, Riverside Clinic, Detroit, Mich.

Many of these patients with a history of multiple hemorrhages were not seen by us during the initial episodes of bleeding. The oldest man to hemorrhage was sixty-four years of age and the youngest was twenty-one years of age. The oldest woman to bleed was seventy-two years of age and the youngest was twenty-three years old. Our data, therefore, concur with that of Tidmarsh in that hemorrhage was more prevalent either for the first time or as a repeated episode in the age groups of the fourth decade and above. The ratio of males to females experiencing hemorrhage from peptic ulcer has been reported as 9.5 to 1.[3] We also found that this condition occurred more frequently in the male than in the female, there being forty-two males to fifteen females in our series, a ratio of 2.8 to 1.

TABLE III
HEMORRHAGE IN MALES IN OUR SERIES ACCORDING TO AGE DISTRIBUTION

Ages	First Hemorrhage		Second Hemorrhage	
	No. Patients	Per Cent	No. Patients	Per Cent
20–24	1	2.38	1	9.09
25–29	2	4.76	2	18.18
30–34	4	9.52	1	9.09
35–39	4	9.52	0	.....
40–44	10	23.80	2	18.18
45–49	10	23.80	1	9.09
50–54	3	7.14	1	9.09
55–59	5	11.90	2	18.18
60–64	3	7.14	1	9.09
Total	42	.....	11	.....

One patient in the age group 50–54 had four separate hemorrhages before coming under our care.

TABLE IV
BODY BUILD OF PATIENTS IN OUR SERIES

Weight	Males	Females	Combined Percentages
Average weight.....	17	5	38.59
Obese.....	11	6	29.82
Tall, slender and undernourished.....	12	4	28.07
Not stated.....	2	0	3.5

Although peptic ulcer is classically stated to occur in the tall, lean, square-jaw, nervous individual, it may be found in individuals of any body build.

From our figures it would seem that body build was not a pertinent factor either in the incidence of ulcer occurrence or predisposition to hemorrhage.

TABLE V
X-RAY FINDINGS OF THE UPPER GASTROINTESTINAL TRACT IN OUR PATIENTS

Lesion	Males	Females
Gastric ulcer.....	7	1
Duodenal ulcer.....	21	5
Combined duodenal and gastric ulcer	1	0
Negative x-ray findings*.....	8	1
None taken†.....	5	8

* X-rays were not taken sooner than two weeks after the bleeding began and the patient had been put on strict ulcer management. It is recognized that the superficial ulceration may have healed during this interim.

† These patients were x-rayed previously in other institutions and the results were made available to us. They were also followed clinically for a sufficient length of time to rule out malignant lesions without x-ray.

There has been considerable debate regarding the time when the patient with bleeding from the upper gastrointestinal tract should be x-rayed. Some clinicians have recommended that the patient have fluoroscopy and x-rays as soon as possible but no manipulation of the stomach or duodenum should be carried out. Other clinicians believe that the patient should be x-rayed two or three weeks after bleeding has ceased. A strong argument against the latter procedure is that the x-ray findings are frequently negative after two or three weeks since healing has taken place on the medical regimen. We have always delayed taking x-rays of our patients for at least two weeks after the bleeding has ceased for fear that undue manipulation of the abdomen might precipitate severe hemorrhage.

We also believe that fluoroscopy carried out without manipulation and x-rays taken at the time of hemorrhage frequently fail to show any gastrointestinal lesion. Any

manipulation of the patient's abdominal wall, stomach or duodenum immediately after hemorrhage is exceedingly dangerous and must be avoided. One of the most severe cases of bleeding from a proven peptic ulcer in our series started approximately ten minutes after the patient's abdomen had been palpated in the course of a routine physical examination. Alvarez[4] has called attention to the fact that severe gastric hemorrhage may be produced by violent abdominal massage.

Rafsky and Weingarten[5] believe that the following factors play a definite rôle in precipitating gastrointestinal hemorrhage: upper respiratory infections, alcoholic beverages, emotional disturbances, dietary in discretions, physical exertion and overwork.

Any bleeding from an ulcer denotes activity of the lesion. Erosion or superficial ulceration of the duodenal or gastric mucosa may cause massive hemorrhages. A penetrating ulcer of either the stomach or duodenum with penetration into the head of the pancreas frequently brings on massive bleeding. A branch of the superior pancreaticoduodenal artery is involved in such an ulcer. Ulcers occurring along the lesser curvature of the stomach also account for many cases of massive hemorrhage because of their proximity to the left gastric artery. It must be stressed that a perforating ulcer will bleed. The mechanism of this bleeding is the erosion of a vessel in an organ to which the ulcer becomes attached, with perforation at the periphery taking place simultaneously.[7]

According to Bockus,[6] the bleeding point in hemorrhagic peptic ulcer is frequently found in the lateral wall of a blood vessel. Thrombosis within the vessel with resulting organization and obliteration of the bleeding point frequently occurs to save the patient's life. In other cases, especially in patients who present considerable arteriosclerosis, the eroded blood vessel lies in the scarred ulcer base as a stiff vessel with its lumen presenting. This does not permit retraction and constriction of the lumen so that fatal hemorrhage may occur.

Most hemorrhages from peptic ulcer do not result from penetration into a large vessel. Rivers and Wilbur[8] have shown that hemorrhage may occur from small congested vessels which surround the ulcerated area or from vessels in the buds of vascular granulation tissue seen in the base of an ulcer. Peptic ulcers tend to heal rapidly following severe hemorrhage. Bockus[6] states that if pain persists following severe bleeding, there is usually continuation of the bleeding and lack of healing in the ulcer.

TABLE VI

GASTROINTESTINAL SYMPTOMS BEFORE FIRST HEMORRHAGE (MULTIPLE COMPLAINTS NOTED IN MOST CASES)

Symptom	No. Patients
Epigastric pain one to four hours after meals which was relieved by food and alkali	39
Exacerbation of epigastric pain after meals in the spring	22
Exacerbation of epigastric pain after meals in the fall	21
"Gas on stomach"	14
Fullness in the epigastrium immediately after eating	9
Epigastric night pain relieved by food or alkali	8
Nausea	5
Belching	4
Vomiting (not blood)	3
Lower mid-abdominal pain	3
Weight loss	3
Constipation	2
Anorexia	2
"Acid stomach"	1
Epigastric tenderness	1
Epigastric pain not relieved by food	1
No complaints mentioned	6

The duration of gastrointestinal symptoms before the first hemorrhage was variable. In our series there was an average lapse of 5.64 years in the case of males and 7.6 years in the case of females from the time of the onset of the first symptoms until the first hemorrhage took place. The longest interval between the initial symptoms and bleeding in the case of a male patient was fifteen years and the shortest duration was two weeks. In one of our female patients the longest interim period was twenty-five years and the shortest was six months. It was not possible in our series of cases to determine accurately the time interval that the patient had had adequate treatment before the first hemorrhage since many patients have

a tendency to follow an ulcer diet only long enough to obtain temporary relief and then attempt a dietary regimen of their own selection. Other patients fail to seek medical advice until gastrointestinal bleeding has actually occurred.

TABLE VII
TIME OF YEAR OF ONSET OF BLEEDING IN OUR PATIENTS (INCLUDING MULTIPLE HEMORRHAGES)

Month	No. Patients
January	9
February	11
March	15
April	10
May	5
June	4
July	1
August	3
September	6
October	11
November	2
December	6

Rafsky and Weingarten[5] in their series of bleeding peptic ulcers noted that the greatest number of hemorrhages occurred from the latter part of October to the latter part of March. This period of time corresponds with the increase of upper respiratory infections. Analysis of our data confirms the observations made by these authors. Eight of our patients noted onset of their hemorrhages between 7 A.M. and 12 noon; two patients noted onset of their bleeding between 12 noon and 11 P.M. and two patients began to bleed between 11 P.M. and 7 A.M.

TABLE VIII
AVERAGE TIME INTERVAL BETWEEN HEMORRHAGES

Sex	First and Second Hemorrhage		Second and Third Hemorrhage	
	Years	No. Patients	Years	No. Patients
Male	3.78	13	6	1
Female	7	7	1	1

In the case of one male patient one year elapsed between the third and fourth hemorrhages. The female patient who hemorrhaged six times had an interim of six months between the third and fourth hemorrhages, two months between the fourth and fifth episodes of bleeding and one year elapsed between the fifth and sixth hemorrhages.

A further study of our cases reveals that once a patient has had hemorrhage from a peptic ulcer there is a strong possibility that he will have recurrence of bleeding. For this reason we are strong advocates of a strict medical regimen which includes adequate follow-up supervision.

TABLE IX
SYMPTOMS AND SIGNS AT ONSET OF GASTRODUODENAL HEMORRHAGES

Symptom	No. Patients
Pallor	46
Tarry stools	39
Emesis of dark blood	30
Weakness	30
Severe epigastric pain relieved by alkali	16
Nausea	15
Syncope	12
Vertigo	9
"Excessive gas on stomach"	6
Emesis of old food (not blood)	5
Emesis of bright red blood	5
Profuse perspiration	4
Diarrhea	4
Shortness of breath	3
Thirst	3
Headaches	1
Abdominal distention	1
Severe chest pain with pain down left arm	1
Anorexia	1
Feverish	1
Double vision	1

The clinical picture at the onset of gastroduodenal hemorrhage varies according to the amount of blood lost. A patient who does not lose more than 350 cc. of blood into the intestinal tract usually does not experience any marked symptoms since the temporary loss in blood volume is quickly compensated for. A patient with such a small loss of blood will experience tarry stools, probably hematemesis of a small amount of blood and will possibly complain of nausea. A patient experiencing a sudden hemorrhage greater than 350 cc. of blood may have hematemesis, an urge to defecate, weakness, nausea, marked perspiration, vertigo and syncope.

If the hemorrhage ceases, these mild symptoms of shock are usually easily overcome. In massive hemorrhages there is, in addition to these findings, evidence of

severe shock with a marked fall in blood pressure, rapid thready pulse, cold and clammy skin, air hunger, marked thirst, anxiety and restlessness. In some patients the loss of blood may be massive yet so slow that the initial complaints are marked weakness, palpitation on exertion and marked pallor of the skin.

Rafsky and Weingarten[5] have advised grading the severity of bleeding according to the lowest recorded hemoglobin value and red blood cell count in each case. If there was overlapping of the values into two grades, the final classification was based on clinical data such as vertigo, syncope, pulse rate, blood pressure, serum proteins, blood urea nitrogen and the amount of bleeding observed during the hospital stay. The classification as used by these authors was as follows:

Grade of Bleeding	Hemoglobin	Red Blood Cells per cu. mm.
Grade I.....	12 Gm. (80%) or above	4,000,000 or above
Grade II.....	9–11.8 Gm. (60–70%)	3,000,000 to 3,990,000
Grade III.....	6.8–8.8 Gm. (45–59%)	2,250,000 to 2,999,000
Grade IV.....	below 6.8 Gm. (below 45%)	below 2,250,000

Such criteria obviate use of such terms in classifying bleeding as profuse, gross, copious and massive, thereby making for a standard with which to judge bleeding.

Using the Rafsky-Weingarten classification of hemorrhage, we obtained the following results:

TABLE X
CLASSIFICATION OF FIRST HEMORRHAGE IN MALES

Grade of Bleeding	No. Patients	Percentage
1	6	18.18
2	9	27.27
3	9	27.27
4	7	21.21
?	2	6.06

In two cases no data were available.

TABLE XI
CLASSIFICATION OF SECOND HEMORRHAGE IN MALES

Grade of Bleeding	No. Patients	Percentage
1	3	25.00
2	5	41.66
3	2	16.66
4	2	16.66

There was one male patient who experienced his fourth hemorrhage and this latter episode was a grade III bleeding.

TABLE XII
CLASSIFICATION OF FIRST HEMORRHAGE IN FEMALES

Grade of Bleeding	No. Patients	Percentage
1	2	20.00
2	3	30.00
3	2	20.00
4	2	20.00
?	1	10.00

In one case no data were available.

TABLE XIII
CLASSIFICATION OF SECOND HEMORRHAGE IN FEMALES

Grade of Bleeding	No. Patients	Percentage
1	1	14.28
2	4	57.14
3	1	14.28
4	0	0.
?	1	14.28

In one case no data were available; one female patient bled six times; no data were available for the third, fourth and fifth hemorrhages and the sixth hemorrhage was classified grade I.

TABLE XIV
CLASSIFICATION OF ALL GROUPS COMBINED

Grade of Bleeding	No. Patients	Percentage
1	13	19.40
2	21	31.34
3	15	22.38
4	11	16.41
?	7	10.44

No data were available for seven cases.

We wish to stress the fact that a patient may enter the hospital with a history pointing toward a recent gastroduodenal hemor-

rhage and yet the initial red blood cell count, hemoglobin and hematocrit may be within normal limits. The laboratory data should not lull one into a sense of false security and make the clinician believe that the hemorrhage was very small for if the laboratory work is repeated within twelve to eighteen hours a marked fall in the values for red blood cells and hemoglobin will often be noted. This is accounted for by the fact that after the initial hemorrhage there has been hemoconcentration and after this has disappeared the blood count, hemoglobin value and hemotocrit fall as a result of hemodilution. Some of our patients who presented initial hemoconcentration proceeded to have a massive hemorrhage while in the hospital, and if adequate blood had not been provided and kept in readiness as soon as the patient entered the hospital, several fatalities might have resulted.

TABLE XV
COMPLICATING DISEASES IN OUR PATIENTS

Disease	No. Patients
Secondary anemia	52
Undernutrition	10
Obesity	9
Hemorrhoids	8
Varicose veins of legs	4
Osteoarthritis, generalized	4
Diverticulosis of colon	3
Pyorrhea	3
Chronic cholecystitis and cholelithiasis	3
Hypertension	3
Inguinal hernia	3
Arteriosclerotic heart disease	3
Pulmonary emphysema	2
Diabetes mellitus	2
Menopausal syndrome	2
Hypertensive heart disease	2
Acute appendicitis	2
Central nervous systemlues (treated adequately)	2
Incisional hernia	1
Arrested pulmonary tuberculosis	1
Chronic sinusitis	1
Acute glomerulonephritis	1
Chronic tonsillitis	1
Senile dementia	1
Generalized arteriosclerosis	1
Benign prostatic hypertrophy	1
Cerebral arteriosclerosis	1
Varicocele	1
Chronic bronchitis	1
Cataracts	1
Hydrocele of the cord	1
Rectal ulcer (benign)	1
Optic atrophy	1
Prolapse of uterus	1
Polyp of sigmoid colon	1
Cervicobrachial fibrositis	1
Tuberculous adenitis	1
Rheumatic heart disease	1

Bockus[6] has shown that hyperazotemia in massive gastroduodenal hemorrhage may result from absorption of the products of digestion of blood proteins or from functional renal impairment. Alimentary hyperazotemia may be used as a gauge of the severity of bleeding in the absence of vomiting or functional renal hyperazotemia. Azotemia expresses the amount of blood protein absorbed from the bowel and parallels the extent of anemia. The maximum rise in the blood urea nitrogen takes place in twenty-four to forty-eight hours after a massive hemorrhage and returns to normal in seventy-two to ninety-six hours if the bleeding has ceased and the kidney function is not impaired.

Fever and toxic symptoms may be noted in hyperazotemia of alimentary origin between the second and fifth day if a large amount of blood is present in the intestine. Functional renal impairment may result in hyperazotemia not due to the absorption of blood protein from the intestines or intrinsic renal disease. Dehydration contributes to the increase in blood urea nitrogen by bringing on oliguria and anuria. A steady fall in the volume of urinary output with adequate fluid intake indicates marked functional impairment of the kidneys and is a bad prognostic sign. The mortality from hemorrhage is high when the blood urea nitrogen is above 100 mg. per cent. The blood urea nitrogen was determined in fifteen of our patients and the average was 54.1 mg. per cent, a value of 14.1 mg. per cent above the highest normal for our laboratory.

The plasma chlorides may be normal or increased in patients not having excessive vomiting. The blood chloride concentration in such cases is influenced mainly by the degree of dehydration. In six of our patients the plasma chlorides were determined and

averaged 559 mg. per cent (normal 550 to 650 mg. per cent).

Other biochemical changes noted in upper gastrointestinal tract bleeding are: hypoalbuminemia, urobilinogenuria, hyperbilirubinemia and a slight icterus, probably a result of an increase in the activity of the reticulo-endothelial cells. Bockus[6] states that the hematocrit is very important as an estimate of the magnitude of hemorrhage, as it will be low after hemorrhage and after the hemoconcentration has been corrected. Seven of our patients revealed an average hematocrit of 23.71 per cent. After hemorrhage the healthy bone marrow may respond with varying degrees of leukocytosis, the average count after gastrointestinal hemorrhage being about 12,000 leukocytes per cu. mm. The average white blood count in forty-six of our subjects was 9,447. The bleeding and coagulation time, prothrombin time and bromsulfalein tests were not performed routinely on our patients but all these tests are normal in the presence of bleeding from a peptic ulcer, except for the coagulation time which is accelerated.

Examination of the stools revealed the following data: Forty-five patients had 4 plus occult blood, in twelve cases no stools were sent to the laboratory and in four instances the stools were negative for occult blood at the time the patient was first seen. An attempt was made to determine the number of days it took from the time of entrance to the hospital until the stool became negative for occult blood. The following results were tabulated:

TABLE XVI

Cases	Days	Cases	Days	Cases	Days
1	2	1	11	1	19
1	5	1	14	1	20
2	6	1	15	1	21
1	8	1	16	1	30
3	9	1	17		
2	10	3	18		

Twenty-one patients were not followed adequately so the exact number of days for the stools to become negative for occult blood was not determined.

At the present time it is our policy not to determine immediately the amount of free hydrochloric acid in the case of a bleeding peptic ulcer because it is not always safe to carry out intubation after a recent upper gastrointestinal hemorrhage for fear of precipitating a gastric hemorrhage or rupturing esophageal varices in cases in which the diagnosis may be questionable. Of the cases reviewed a small number of patients did have a free hydrochloric acid determination before we realized the possible dangers resulting from this procedure. The results were as follows:

TABLE XVII

Degrees of Free Hydrochloric Acid	No. Cases
Trace (exact amount not stated)	4
6	1
7	1
17	1
18	1
30	2
52	1
Degrees not stated	11

No determination of free hydrochloric acid was done in thirty-six cases.

Serologic study is always important in determining if an upper gastrointestinal lesion is on a luetic basis since most patients with syphilis of the stomach have positive tests. In our series of reviewed cases there were fifty negative blood serology tests. Five were not done, two patients had previously had positive Kahn and Kline tests, had received adequate antiluetic therapy and were serologically negative upon entering the hospital. One patient had 4 plus Kahn and Kline tests on entrance to the hospital.

It has been our policy to hospitalize our patients as soon as we suspect that there has been blood loss into the bowel. Without further delay a careful history is taken and a thorough physical examination is completed, avoiding excessive palpation of the abdomen. The patient's blood is immediately typed and cross-matched so that blood can be made available in large amounts at any hour of the day.

In addition to this the following laboratory data are obtained: (1) red and white blood cell counts; (2) hemoglobin determination; (3) differential count; (4) serology; (5) urinalysis and (6) a hematocrit in many cases. A stool specimen is sent to the laboratory for complete analysis. If the hemorrhage has been profuse, an initial blood chloride and blood urea are usually determined. A blood platelet count, prothrombin determination, bleeding and coagulation times and a bromsulfalein test are performed if we suspect the cause of bleeding to be a result of a hematologic disturbance or combined spleen and liver disease.

Our plan of medical treatment consists of feeding the patient immediately, giving him a Sippy diet with aluminum hydroxide as the antacid. In addition the patient is given supplements of vitamins plus broiled hamburger or scraped beef twice a day. After a period of one to two days supplementary feedings are added in order to increase the patient's caloric intake. By means of this diet we attempt to keep the patient from loading his stomach to an excess at any one feeding yet he is given enough food to satisfy his hunger and to allow for an adequate caloric and vitamin intake. By following this procedure the free hydrochloric acid is diluted and motor activity of the stomach reduced. Early feeding was advocated in 1904 by Lenhartz[9] who gave his patients milk and eggs from the time of admission and scraped beef on the sixth day. He noted that the body depletion and anemia were overcome more rapidly by this means.

Later Andresen[10] recommended immediate feeding using gelatin mixtures. With this regimen, there was a reduced mortality in his patients with gastrointestinal bleeding. LaDue,[11] using Andresen's diet, noted a sharp decrease in the mortality in the patients treated by this method. Early feeding became popular in this country after 1933 when Meulengracht[12] advised a diet of early and liberal feedings. It was thought that the regenerative processes were promoted, the patient became stronger, the anemia was overcome and the mortality and morbidity were decreased.

We are strong advocates of the policy of transfusing only when indicated by the patient's clinical and laboratory findings. Patients who have grade I bleeding obviously do not need a transfusion providing that the bleeding ceases soon after the patient enters the hospital. Patients with grade II bleeding may or may not need blood. We usually begin to administer small transfusions whenever the hemoglobin has fallen to approximately 10.5 Gm. and the red blood cell count to 3,750,000. Patients with grade III and grade IV bleeding are routinely transfused. When no emergency exists the blood is given slowly, usually in the amounts of 250 cc. per transfusion and is repeated until the blood determination reaches a hemoglobin of 12 Gm. and 4,000,000 red blood cells.

An occasional patient may go into shock so rapidly that the blood must be given quickly to avoid irreversible tissue changes. Such subjects may be given plasma until blood becomes available. With this type of case, blood is given until the patient is no longer in shock as judged by clinical criteria after which small transfusions are resumed. An occasional patient may continue to bleed slowly so that life-endangering exsanguination may take place. In both the slowly and rapidly bleeding patients falling into group IV we have given up to 1,000 cc. of blood over a twenty-four-hour period for from one to two days. We do not hesitate to exceed this amount if necessary.

Blood transfusion for bleeding ulcer has always been and remains a controversial subject. Those who advocate no blood unless the red blood cell count is 2,500,000 or less maintain that transfusions will raise the patient's blood pressure and dislodge any clots that may have formed at a bleeding point, thereby increasing the extent of the hemorrhage. Those clinicians who advocate early transfusions believe that there is no danger either in the amount or the rate of transfusion. Bohrer[7] in his series of cases stated that transfusions were given for

massive gastric hemorrhage in the amounts of 500 to 1,000 cc. and that no secondary hemorrhages were noted.

Jones[13] has administered slow transfusions in amounts up to 2,650 cc. daily, without a rise in the blood pressure. Since massive upper gastrointestinal bleeding tends to cause hypoproteinemia, blood transfusions are given to replace the valuable proteins and the red blood cells tend to overcome tissue anoxemia, both factors playing a large part in preventing further bleeding by aiding tissue healing. Recently Levy[14] has called attention to the importance of hypoproteinemia resulting from bleeding peptic ulcer and has noted a beneficial effect from the administration of amino acids.

In addition to the diet and blood therapy, sedation is used routinely but the amount varies. On the type of diet which we have recommended the patient receives ¼ gr. (0.016 Gm.) of luminal three times a day in combination with belladonna.

If an excessive amount of retching occurs or the patient is unduly restless and apprehensive, sodium luminal is given intramuscularly in the dose of 2 gr. (0.13 Gm.) every three to four hours as needed. Morphine and other narcotics have not found favor with us because of the frequently associated nausea, vomiting and anorexia which follows.

Considerable attention must be given to the bowels inasmuch as our diet is very constipating. A small saline enema is given every second to third day. In addition to avoiding fecal impaction this will rid the bowel of the broken-down digestion products of the old blood which many clinicians believe cause a toxic reaction and fever in the first three to five days of the illness. Emphasis is placed upon the fact that psychotherapy is a very important and integral part of treatment in any type of ulcer patient but particularly so with the patient with a bleeding ulcer who frequently is very apprehensive and under great stress.

We present the following three histories to illustrate the application of our medical regimen which has been described. It should be noted that these patients were extreme examples of grade IV bleeding who were very difficult to handle. Emphasis is placed on the part played by early feeding plus large amounts of blood in achieving successful therapy.

CASE REPORTS

CASE I. M. B., a male, was first seen on May 27, 1945, at which time he stated that he had had "stomach trouble" for one month. The onset of his illness was characterized by midline epigastric pain and gaseous distention. These appeared about one-half hour after eating and were relieved by milk of magnesia or soda bicarbonate. The abdominal pain radiated to his back and the vicinity of the right scapula. He was seen by a doctor who made a diagnosis of gallbladder disease for which he was treated. He appeared to improve on a medical regimen when suddenly two days before being hospitalized while at work he vomited what he believed to be 1 pint of dark red blood. He then developed the back pain but no longer had the epigastric distress. One day prior to entering the hospital he again had a sudden emesis of what he believed to be 1 pint of dark blood. He had lost 10 pounds of weight in five weeks. The patient was immediately hospitalized. There was no history of abdominal trauma or excessive indulgence in alcohol. The past history was noncontributory.

Physical examination revealed an acutely ill, undernourished, white male of forty-four years of age. His height was 5 feet 9 inches and he weighed 135 pounds. His skin was warm, dry and had lost its turgor. The rest of the examination was negative.

Laboratory work done upon entrance to the hospital showed the following: urine was negative; hemoglobin was 58 per cent; red blood cell count was 2,750,000; white blood cell count was 5,350 and the color index was 1.05. The differential count revealed 72 per cent polymorphonuclear neutrophiles of which 70 per cent were filamented and 2 per cent were nonfilamented. There were 28 per cent lymphocytes. The red blood cells showed moderate anisocytosis. The Kline test was negative. The stool specimen was tarry-colored and gave a 4 plus reaction for occult blood. The blood urea was 97.7 mg. per cent, the blood chlorides were 503 mg. per cent and the carbon dioxide com-

bining power was 61 volumes per cent. The bromsulfalein test did not reveal any dye retained at the end of one hour. A chest x-ray revealed a healthy chest.

The patient's course in the hospital was very stormy. He was put on hourly feedings of milk and cream from 7 A.M. to 7 P.M. and again at 2 A.M. and 5 A.M., with supplementary feedings of broiled hamburger twice a day. Atropine gr. $\frac{1}{150}$ (0.0004 Gm.) by hypodermic was given until there was dryness of the mouth and visual disturbances. The patient was also given sodium luminal gr. 2 (0.13 Gm.) intramuscularly every four to six hours. In addition he received large doses of vitamins parenterally. On this regimen he continued to be nauseated and vomited large amounts of dark red blood. With each emesis, he had symptoms of mild shock for which he was given 250 cc. of plasma the first day, 500 cc. of blood the following day and 250 cc. of blood the third day. On the fourth day two blood transfusions of 250 cc. each were administered and on the fifth day he was given 750 cc. of blood. With all this parenteral therapy his laboratory data showed 30 per cent hemoglobin and a red blood cell count of 1,460,000.

Since the situation seemed to be rather desperate for the patient, it was decided to give him large amounts of blood slowly and continuously. On June 1st he was given 1,000 cc. of blood after which he began to feel better, retained his diet and was no longer nauseated. The blood data on this day revealed a hemoglobin of 44 per cent and a red blood cell count of 2,100,000. He was given 500 cc. of blood daily for the next five days and continued to feel well and improve clinically. On the sixth day after this intensive therapy the hemoglobin was 83 per cent and the red blood cell count was 4,120,000. Two days later the patient was up and about. A gastrointestinal x-ray (without abdominal manipulation) on June 13th was interpreted as being suspicious for a small duodenal ulcer. He was discharged from the hospital on June 14, 1945, and has felt well since.

CASE II. S. N., a forty-seven year old male, entered the hospital on February 3, 1945, in a state of shock. He stated that an hour previous to his entrance he had begun to vomit large amounts of dark red blood. He was immediately given 250 cc. of plasma which was followed by 250 cc. of red blood cells suspended in saline. There was a dramatic response and his blood pressure rose; he became alert and was no longer cold and clammy.

Careful questioning then revealed that for the past three years he had complained of "indigestion" which first began as a midline epigastric cramping pain that began one-half hour after meals. Taking soda bicarbonate and amphogel wafers relieved the pain. The pain never awakened him at night. Since this initial onset of pain, he began to complain of vague abdominal discomfort stating he "bloated" immediately before and after meals. He did not know whether taking food relieved his epigastric pain or not. For the past three weeks he had felt a gradual loss of strength and an inability to do heavy work.

On the day of entrance to the hospital, while at work, he suddenly became very warm, felt nauseated and had an urge to defecate. He suddenly fainted after vomiting dark red blood and when he regained consciousness the vomiting of dark red blood began again. There was no previous history of tarry stools nor was there any history of consumption of an excess of alcohol. The patient had been treated adequately for syphilis; otherwise, the past history was non-contributory.

Physical examination upon entrance to the hospital revealed the following: the patient was 5 foot 8½ inches tall and weighed 145 pounds. His pulse rate was 120 and his blood pressure 70/50. He was very restless and his skin was cold and clammy. His lips were covered with fresh blood. His abdomen revealed a slight tenderness in the epigastric area but there was no rigidity. The liver, spleen and kidneys were not palpable.

Laboratory data revealed the following: Hemoglobin was 65 per cent (10 Gm.); the red blood cell count was 3,360,000, the white blood cell count was 17,200 and the color index was 0.99. The differential smear revealed 76 per cent polymorphonuclear cells, 53 per cent being filamented and 23 per cent non-filamented, 23 per cent lymphocytes and 1 per cent monocytes. The urine was negative as was the Kline test. The blood urea was 113 mg. per cent, the blood chlorides were 578 mg. per cent and the carbon dioxide combining power was 50 volumes per cent.

The patient was put on the same diet as was used in Case I, with adequate vitamins. No gastric analysis was carried out. The patient felt well until 4:30 P.M. on February 4th when he suddenly began to vomit large amounts of

dark blood, his skin became cold and clammy and he had a desire to defecate. His stools were tarry. The patient was immediately given 500 cc. of plasma and 500 cc. of whole blood but his condition did not improve. He continued to vomit, his skin was cold and clammy and his bladder and bowels were incontinent. Because of the gravity of the situation, it was decided to place a No. 18 gauge needle in each antecubital vein and to administer whole blood and saline suspensions of red blood cells continuously. The patient received 1,500 cc. of whole blood throughout the night and was given 2,300 cc. of whole blood and 300 cc. of red blood cell suspension during the following day. At approximately 6 P.M. (on February 5th) a marked improvement was noted in his condition. His blood pressure had risen to 108/72 but his pulse continued at a rate of 120 per minute. He was having frequent tarry stools but could retain his diet. Laboratory data revealed a hemoglobin of 60 per cent (9.3 Gm.), 3,480,000 red blood cell count and a hematocrit of 29 per cent.

Because of the marked anemia, he was given 400 cc. of red blood cell suspension on February 6th. On this same date there was a rise of temperature to 104 degrees and a diagnosis of pneumonia was made clinically and by x-ray. Recovery was successful with sulfadiazine therapy. On the following day the patient received 1,000 cc. of red blood cells and transfusions were continued the next day in the amount of 500 cc. of red blood cells. The last three transfusions were given slowly as there was no emergency. On February 8th, the last day of transfusions, his hemoglobin was 80 per cent (12.5 Gm.) and the red blood cell count was 4,280,000. The blood urea had fallen to 36.3 mg. per cent. The patient was discharged from the hospital on March 13, 1945, and has continued to feel well since.

CASE III. W. M., a male, was brought to the hospital on October 6, 1945, and gave the following history: Approximately eight years before he noted tarry stools and was told that he had a gastric ulcer. He responded well to conservative medical therapy. Three months previous to entering the hospital he had a cholecystectomy from which he made an uneventful recovery. About two months ago the patient began to develop cramp-like pains in the lower abdomen and also in the epigastrium. He did not recall if the pains were noted after meals or if they were relieved by food or alkali. He also noted excessive flatulence.

Two days before admission to the hospital the patient observed tarry stools of one day's duration. He also had been experiencing double vision and weakness for the past two days. On the day of admission he had vomited dark red blood. The patient also remarked that for the past month he had become increasingly nervous. The past history revealed that he had received adequate antiluetic therapy fifteen years previously.

Physical examination revealed the following: the pulse rate was 110 and the blood pressure 88/58. The patient was an obese white male of fifty-five years of age who was very pale and appeared restless. His pupils reacted to accommodation but not to light. The abdomen revealed slight epigastric tenderness. Laboratory data upon admission to the hospital revealed examination of the urine to be negative, a hemoglobin of 54 per cent and a red blood cell count of 3,000,000.

This patient was also put on a dietary regimen as described in Case I, plus adequate vitamins. No gastric analysis was done at this time but an Ewald test meal one year previously showed 24 degrees free hydrochloric acid. In addition small transfusions of 200 to 350 cc. of blood were slowly administered daily. On the third day of hospitalization after receiving 950 cc. of blood the blood count was 46 per cent hemoglobin and 2,250,000 red blood cells. On the following day it was decided that the patient's condition was becoming worse and therefore larger transfusions, each averaging 500 cc., were given. On October 15th, after receiving a total of 2,250 cc. of blood, the blood count was 2,260,000 red blood cells and 46 per cent hemoglobin. The patient was having tarry stools daily. The same day small transfusions of 250 cc. daily were resumed but by five days later the hemoglobin had fallen to 35 per cent and the red blood cell count was 1,960,000 in spite of an additional 1,000 cc. of blood.

Because of the patient's critical condition, it was deemed necessary to give him large amounts of blood. As a consequence a No. 18 gauge needle was inserted into the vein of the left antecubital fossa and whole blood was ordered continuously with at least 1,000 cc. to be given within the first twenty-four-hour period. On October 23rd, after receiving 1,500 cc. of blood, the patient's hemoglobin was 74 per cent with

a red blood cell count of 3,920,000. For the first time since entering the hospital his stools were brown and he felt well. In view of the fact that the emergency had passed it was decided to discontinue giving blood around the clock and the patient received his last transfusion of 500 cc. on this date. A week later the hemoglobin was 81 per cent with a red blood cell count of 4,310,000. The patient was discharged on November 3, 1945, and adequate follow-up has indicated that he has had no difficulties since leaving the hospital.

TABLE XVIII
NUMBER OF HEMORRHAGES PER PATIENT*

Sex	No. Hemorrhages	No. Patients
Female	1	9
Female	2	7
Female	3	1
Female	4	1
Female	5	1
Female	6	1
Male	1	31
Male	2	12
Male	3	1
Male	4	1

* Includes patients with multiple hemorrhages.

TABLE XIX
AMOUNT OF BLOOD GIVEN FOR EACH HEMORRHAGE

Sex	No. Hemorrhages	No. Patients Receiving Transfusions	Total No. Transfusions	Average Amount of Blood per Transfusion per Patient	Average Amount of Blood Received per Patient
Female	1	6	12	310 cc.	620 cc.
Female	2	5	28	305.35 cc.	1710 cc.
Female	3	0	0	0	0
Female	4	0	0	0	0
Female	5	0	0	0	0
Female	6	0	0	0	0
Male	1	25	105	453.80 cc.	1906 cc.
Male	2	7	51	366.66 cc.	2671.42 cc.
Male	3	0	0	0	0
Male	4	0	0	0	0

A total of forty-seven series of transfusions was given to our patients: forty-six of these were administered slowly and one series was administered rapidly to begin with, after which small, slow transfusions were given.

There were four male patients who received plasma infusions. These patients were all experiencing their first hemorrhages. A total of six infusions was given, the total amount of plasma per infusion being 250 cc. and the total amount of plasma received per patient was 375 cc.

In analyzing our data presented in Tables XVIII, XIX and XX a total of 196 transfusions were administered for an average of 358.95 cc. per transfusion. This exceeds the average size transfusion of 250 cc. which is usually recommended. Since some of our patients were in shock and others entered the hospital markedly anemic, it was deemed necessary to give larger transfusions than the average. The average total amount of blood received per patient in our series equaled 1,726.85 cc. whole blood. The average size red blood cell transfusion was 471.05 cc., and the average total of red blood cells received per patient was 1,325 cc. In the case of one patient it was necessary to give 2,450 cc. of red blood cells, 4800 cc. of whole blood and 750 cc. of plasma. The average red blood cell count per patient at the time of discharge from the hospital was 4,266,153 and hemoglobin 69.6 per cent (10.08 Gm.)

TABLE XX
AMOUNT OF RED BLOOD CELLS GIVEN PER HEMORRHAGE*

Sex	No. Hemorrhages	No. Patients Receiving Transfusions	Total No. Transfusions	Average Amount of Red Blood Cells per Transfusion	Average Amount of Red Blood Cells Received per Patient
Female	1	1	6	250 cc.	1500 cc.
Female	2	1	4	250 cc.	1000 cc.
Female	3	0	0	0	0
Female	4	0	0	0	0
Female	5	0	0	0	0
Female	6	0	0	0	0
Male	1	4	12	537.5 cc.	1612.5 cc.
Male	2	0	0	0	0
Male	3	0	0	0	0
Male	4	0	0	0	0

* Red blood cells administered as a saline suspension.

There is considerable debate as to whether emergency surgery should be performed on the patient with a massive hemorrhage from a peptic ulcer. Bockus[6] states that most clinicians prefer to follow the advice of Rodman who recommended that surgery not be performed during an active hemorrhage, with rare exceptions.

The latter author thought that surgery was contraindicated since no definite diagnosis was usually made at the time of the hemorrhage and, therefore, that surgery was usually of no avail. He also believed that the patient who had a severe hemorrhage was a poor surgical risk and pointed out that recovery is frequently the rule without surgery.

Finsterer, quoted by Bockus,[6] has been an advocate of surgery in the case of bleeding from the upper gastrointestinal tract. He operated upon seventy-eight patients who were good risks, defining the latter as those patients operated upon twenty-four to forty-eight hours after the initial bleeding began. He performed a subtotal gastric resection in seventy-one of his patients with four deaths (5.41 per cent mortality). He also performed subtotal gastric resection in sixty-three patients who had bled, the operation being performed forty-eight hours or longer after the initial hemorrhage. In this series of cases the mortality rose to 26.9 per cent. Those who have analyzed Finsterer's statistics have thought that the latter series would have yielded better results with medical management inasmuch as not more than 10 per cent of the patients with massive hemorrhage will usually die after medical treatment. As for low mortality in the cases of early bleeding it is unwise to subject all such patients to surgery since many may be easily controlled with medical management. Bockus[6] believes that individualization in the selection of patients submitted to surgery is important. He advocates use of conservative therapy for a brief period of time and if the hemorrhage has been severe, the normal blood volume cannot be maintained and all the signs point toward continued bleeding then surgery must be considered. If such a patient is fifty years of age or older and gives a long history of ulcer symptoms, then additional weight is given in favor of surgical intervention. He also believes that patients who have an exacerbation of their severe hemorrhage several days after a first hemorrhage should be submitted to surgery if it is not possible to maintain their normal blood volume.

Held[15] believes that elective surgery should not be carried out after only one hemorrhage unless the patient must be away on long journeys from a place where he could safely obtain adequate medical or surgical care. A second hemorrhage within six months to a year is sufficient ground to advise surgical intervention after the second hemorrhage. After a third hemorrhage surgery should be carried out regardless of circumstances. Surgery is also recommended if occult blood appears in the stool intermittently and in sufficient quantities to account for a secondary anemia. In the latter case it is believed that frequent oozing should make one suspicious of the development of a malignant lesion. Moreover, the continued bleeding from the ulcer lowers the tissue resistance so that healing becomes impossible and perforation may take place.

Hunt[16] believes that patients who are fifty years of age or older and who have recovered from a massive hemorrhage should be subjected to surgery. In our series no patients were treated surgically for bleeding from the upper gastrointestinal tract. No female patient had any form of surgery of the stomach or duodenum previous to her hemorrhage. Two male patients had gastroenterostomies, one male had a pyloroplasty and one patient had emergency surgery for closure of a ruptured gastric ulcer before the hemorrhage. It is of interest to note that two of our male patients had massive hemorrhages three months after a cholecystectomy.

The mortality figures collected from various clinics and hospitals in this country and abroad are not adequate to establish a definite mortality figure. In some statistical papers many cases may be excluded since there is doubtful evidence of peptic ulcer. In other cases only massive hemorrhages have been reported with a high mortality, whereas other authors have recorded only episodes of minor bleeding. There is some general agreement in the mortality statistics from large city hospitals where only massive

hemorrhages were considered. The mortality in such cases is roughly 10 per cent. The mortality figures for ulcer hemorrhages are also unreliable since some clinicians have excluded certain fatalities from their lists for various reasons.[6]

The following factors influence the prognosis of massive hemorrhage from the gastrointestinal tract:

(1) It has been noted that there is a much lower mortality in bleeding ulcers in the female. (2) The age factor is one of the most important in determining the outcome for the patient, most deaths occurring after the age of forty-five. (3) There is a definite higher incidence of deaths from first hemorrhages. In one series 78 per cent of the deaths were reported to have resulted from the first hemorrhage.[17] (4) Antecedent dyspepsia or ulcer-like symptoms definitely give a worse prognosis for bleeding ulcer patients. It has been suggested that in those without previous ulcer symptoms the bleeding is due to a superficial ulcer or erosion rather than to a deep ulcer. (5) Arteriosclerosis is stated to be a definite factor in the prognosis since the older patients bleed from ruptured, stiff vessels which do not retract and tend to stop bleeding. (6) It has been stated that a patient showing a blood urea nitrogen of 100 mg. per cent or more or those patients in whom the loss in cell volume exceeds 50 per cent the prognosis is definitely worse.[6] (7) Hypertension. (8) Erosion into the pancreas and bleeding from granulation tissue in the base of the ulcer have been stated by Schenken[18] to be definite factors in giving a worse prognosis in these cases.

COMMENTS

Fifty-seven cases of bleeding from the upper gastrointestinal tract without a death have been presented. These represented all the case records available to us in which the cause of the bleeding was considered to be benign peptic ulcer. The diagnosis in each case was consistent with peptic ulcer as determined by x-ray and/or clinical and laboratory data. The patients considered were either seen for their initial hemorrhage or were being treated for a repeated episode of bleeding.

In the case of twelve patients no x-rays were taken but previous x-rays had been taken elsewhere and the results were made available to us. Eight patients had negative x-rays but had been on strict ulcer management for two weeks or more so that healing probably had taken place.

The combined age incidence of both the men and women in our series at the time of onset of their hemorrhage, either as an initial or repeated incidence, shows that sixty-one hemorrhages took place when the patient was in the age group of forty years or older.

Using the Rafsky-Weingarten classification for the severity of hemorrhage, it will be noted that twenty-six or 43.33 per cent of our patients had grade III or IV bleeding which is a massive hemorrhage. Forty of our patients had hemorrhages for the first time. The average duration of gastrointestinal symptoms was 5.64 years for the males and 7.6 years for the females. Taking all these factors into consideration, one would certainly expect some fatalities. Again we wish to stress the fact that if the red blood cell count falls to 3,750,000 and the hemoglobin to 10.5 Gm., we give small transfusions of 250 cc. until the hemoglobin is 12 Gm. or greater and the red blood cell count is 4,000,000 or greater. If the patient enters in or develops shock while in the hospital, blood is given rapidly until the shock is overcome; then small transfusions are resumed as long as there is no emergency and the patient maintains his blood volume. If the patient continues to lose blood slowly and this is not replaced by small transfusions, then large amounts of blood are given slowly until the patient's blood volume is maintained at a high level, after which small transfusions are continued.

CONCLUSIONS

1. An analysis of fifty-seven cases of gastroduodenal hemorrhage as the result of peptic ulceration is presented. There were no fatalities in our series. There were thirty-nine patients with duodenal ulcer and

nineteen with gastric ulcer, giving a ratio of 2.05 to 1.

2. Hemorrhage from peptic ulceration may take place at any age but it occurred more frequently in the fourth and fifth decades of life in our series. This has been the observation of other clinicians.

3. Bleeding from the upper gastrointestinal tract as a result of benign ulcers occurs more frequently in men than in women. In our series there were forty-two males and fifteen females, a ratio of 2.8 to 1.

4. Body build was not a pertinent factor in the occurrence of ulcer nor was it a factor in predisposition to hemorrhage in the cases reviewed.

5. We strongly advocate that patients with bleeding from the upper gastrointestinal tract not be x-rayed until at least two weeks have elapsed after the onset of their hemorrhage.

6. Factors precipitating gastrointestinal hemorrhage are: (1) upper respiratory infections; (2) alcoholic beverages; (3) emotional disturbances; (4) dietary indiscretions and (4) physical exertion and overwork.

7. The period from October to March is stated to be the time interval during which most hemorrhages from benign ulcer occur. This was confirmed in our series.

8. From an analysis of our figures it is apparent that there is a great tendency for a patient to have repeated hemorrhages after the initial episode of bleeding.

9. Using the Rafsky-Weingarten classification for the grade of bleeding from a peptic ulcer, there were twenty-six cases (43.33 per cent) classified either as grade III or IV bleeding.

10. The biochemical changes noted following gastrointestinal bleeding are (1) alimentary hyperazotemia; (2) hyperazotemia as a result of functional renal impairment; (3) increase in plasma chlorides, (4) hypoalbuminemia, (5) urobilinoginuria and (6) hyperbilirubinemia.

11. We have outlined the management of upper gastrointestinal hemorrhage. Strong emphasis is placed upon early feeding and large amounts of blood when indicated. Three cases of grade IV bleeding were presented as well as the management and progress of these patients. Continuous and massive blood transfusions are not only life saving but innocuous.

12. We have not had any experience with emergency surgery in bleeding peptic ulcer. Before surgery is attempted we believe that conservative treatment should be carried out.

13. The mortality in bleeding peptic ulcer is determined by the following: (1) sex; (2) age; (3) number of hemorrhages; (4) chronicity; (5) arteriosclerosis; (6) marked elevation of blood urea and decrease of cell volume to 50 per cent or lower; (7) hypertension; (8) erosion into the pancreas and (9) bleeding from granulation tissue in the base of an ulcer.

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Metabolic Studies in Cushing's Syndrome*

Treatment with Various Androgens and a Six-year Follow-up

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In the sixteen years which have elapsed since Cushing[5] described the clinical syndrome now bearing his name a considerable volume of literature has accumulated relative to the diagnosis and treatment of this condition. Numerous types of therapy have been advocated. In those instances in which a pituitary or adrenal tumor could be demonstrated surgery has resulted at times in some clinical improvement and occasionally in remission or cure of the disease.[36] Similar claims have been made for x-ray therapy applied to the pituitary and adrenals or radon seeds implanted into the sella turcica.[23]

Encouraging results have been claimed for estrogens[4,9,14,22] as well as for androgens.[1,2] Albright,[1] who originally suggested the use of testosterone propionate, believed that the disease was associated with or caused by a hypergluconeogenesis at the expense of body protein. Many of the clinical manifestations were thought to be the result of decreased protein availability, for example, muscular weakness, thin skin, easy bruisability and osteoporosis. In metabolic studies on three patients he was able to show, among other findings, a negative nitrogen and phosphorus balance as well as increased urinary calcium excretion. Because of its ability to cause storage of nitrogen, testosterone propionate was selected as a therapeutic agent and his patients received a trial of this substance. Clinically, there was symptomatic improvement as shown by increase in strength and weight, diminished redness of the skin and loss of easy bruisability. Furthermore, the patients promptly stored large quantities of nitrogen as well as phosphorus, the excessive excretion of urinary calcium was checked, calcium absorption improved and the balance became positive. Estrogen therapy failed to exert a beneficial effect on nitrogen, phosphorus and calcium balances in two cases.

Perloff et al.[24] studied a woman with Cushing's syndrome using calcium gluconate, vitamin D_2, testosterone propionate, estradiol benzoate and diethylstilbestrol. Following administration of testosterone propionate, there was retention of nitrogen and phosphorus but with prolongation of treatment for 123 days the nitrogen excretion returned to approximately control levels. Calcium retention was demonstrated with vitamin D_2 but not with the other steroids used. Subjectively, at the end of the period of study the patient noticed an increase in muscular strength and improvement in backache. Objective findings included deepening of the voice, enlargement of the clitoris, increase in facial acne and hirsutism, amelioration of diabetes and some recalcification of the spine. Deakins et al.[6] observed retention of nitrogen with androgen therapy but neither with this treatment nor with estrogens was clinical improvement noted. Their periods of treatment were short and the patient did not present all of the findings characteristic of advanced Cushing's syndrome. In Whitelaw's case[35] administration of testosterone propionate resulted in increased strength

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but was without effect on hypertension, osteoporosis or calcium excretion.

The purpose of the present paper is to present metabolic data on a young female patient with Cushing's syndrome and to evaluate androgen therapy in the light of six years' observation of the patient.

CASE REPORT

J. D. was a fifteen year old white girl who was admitted to the hospital on July 21, 1941, complaining of backache and of being overweight. (Fig. 1.) She had considered herself well until seven months previously when she first noted some pain in her back after jumping over a wooden horse in gymnasium. Following a brief period of rest, she was symptom-free for about five months when she again complained of backache while carrying a pail of water. Weakness gradually developed in her legs and trouble was experienced in getting in and out of bed. Three days prior to admission while stooping to wash her face she had such intense pain in her back that she screamed.

During the previous two years gain in weight had been rapid. Her first menstrual period occurred six months before admission. This was followed by five months of amenorrhea. After receiving a course of estrogens from her local physician (amount unknown) she had another period one month before admission. She also had noted thinning of the hair on her head as well as some increased growth of hair on her face. She suffered bruises easily and it was her impression that her head and face seemed to have increased in size. She also had noted that her arms and legs seemed disproportionately thin in comparison with the rest of her body.

The patient's past history revealed that she had been born prematurely weighing 4½ pounds at birth; she walked late at the age of twenty-two months. Development was otherwise apparently normal until the onset of gain in weight two years previously. Other members of the family seemed normal except that the mother was quite obese. An older brother and sister were in good health.

Physical examination revealed the following: Temperature 37°c., pulse 72, respiratory rate 16; blood pressure 146/92; height 148 cm., weight 54.3 Kg. Her general appearance was rather striking; she was obese and appeared older than her stated age. There was excessive

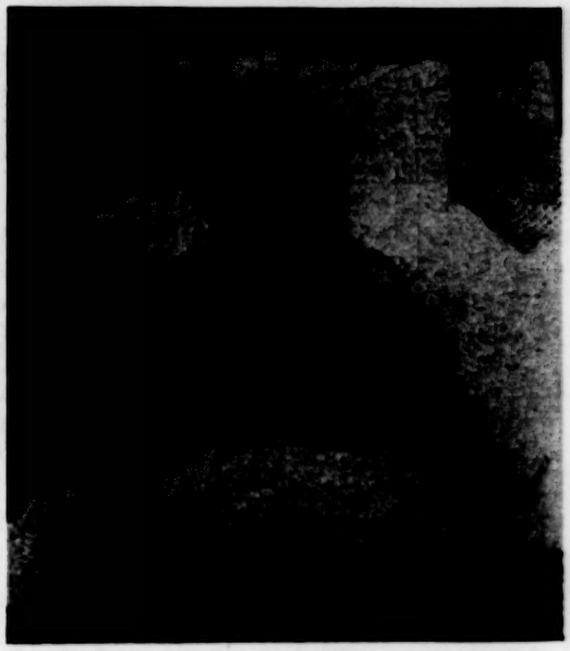

FIG. 1. Patient J. D., aged fifteen, at time of first admission.

rubicundity with a full-moon face and "buffalo" distribution of the obesity as well as a conspicuous roll of fat beneath her chin. The facial hair was excessive while that on the scalp was thin and of fine texture with partially bald areas. The skin was very thin over the extremities with a mottled, cyanotic hue. Over the anterior abdomen, flanks and upper thighs many wide red or purplish striae with smooth, shiny, paper-thin surfaces were seen. The axillary and pubic hair was sparse and coarse; the latter had a male type of distribution. The neck appeared unusually short so that the head seemed to rest on the shoulders. The dorsal kyphos was exaggerated and tenderness was present over the right iliac crest. Weight-bearing was very painful with complaints referable to the lumbar spine. The visual fields and fundi were normal. She had moderately severe dental caries. The breasts were small and poorly developed; the heart, lungs and abdomen were not remarkable; the genitalia were normal for a girl of her age.

Laboratory data revealed the following: Blood Wassermann test, negative. Blood: red blood cell count, 5,900,000; hemoglobin, 19.6 Gm./100 cc.; white blood cell count, 9,200. The differential formula was normal. Stool examination: light brown, formed, guaiac negative. Urine examination: specific gravity, 1.020; albumin 0; sugar, 0. Microscopic examination negative and cultures sterile. Phenolsulfonphtha-

lein excretion test, 90 per cent in two hours. Blood chemistry: whole blood contained non-protein nitrogen, 34 mg.; sugar, 67 mg./100 cc. The serum contained for each 100 ml.: total proteins, 6.2 Gm.; albumin, 4.2 Gm.; globulin, 2.0 Gm.; calcium, 9.3 mg.; phosphorus, 3.6 mg.; alkaline phosphatase, 8.7 Bodansky units; acid phosphatase, 3.5 King-Armstrong units and cholesterol, 261 mg. For each L. of serum there were: chloride, 101 mEq.; carbon dioxide, 26 mEq. and potassium, 4.3 mEq. (For sugar tolerance tests, urinary neutral 17-ketosteroids, creatine and creatinine and basal metabolism *vide infra.*) The results of a glucose insulin tolerance test[12] were as follows:

Time (min.).	Fasting	20	30	45	60	90	120
Blood sugar (mg. per cent).....	95	156	155	154	151	142	118

Follicle-stimulating hormone: less than five mouse uterine units per twenty-four hours.[32]

Microscopic examination of uterine curettings and skin: The pelvic examination was done under anesthesia. The cervix and uterus were unusually small. Curettings revealed a resting endometrium. Biopsy of the skin of abdominal stria: "Normal skin thins out gradually with lessening of elastic fibrous tissue until hardly any elastic tissue is present. Few skin glands are seen."

X-ray reports revealed that the sella turcica was not enlarged in two examinations. There was decalcification of the bones of the forearms, lumbar spine and pelvis with collapse of the vertebral bodies of the lower dorsal and upper lumbar spine. Bilateral perirenal air insufflation did not reveal enlarged adrenals. No abnormality of the renal pelves was found by retrograde pyelography.

On September 13, 1941, she was transferred to the metabolic unit for the purpose of investigating the effects of androgens (*vide infra*). Following this she was given additional daily injections of testosterone propionate. Because of the severe osteoporosis of the spine and resulting pain in the back, abdomen and thighs, she was confined to bed most of the time at first but by February, 1942 was able to be up part of the day. Late in September, 1941 she began to have blurring of vision and ocular pain, occasional at first but gradually increasing, until by May, 1942 the existence of chronic glaucoma was definite. In June a bilateral Elliott trephine operation was carried out which relieved her symptoms considerably.

She was discharged on November 21, 1942, having received 4,865 mg. of testosterone propionate intramuscularly. Pains had subsided somewhat but her blood pressure had increased to an average of 190/130, marked hypertensive changes had occurred in the retinal vessels and headaches were more pronounced. Her weight was the same as on admission. She was able to go to school. A large part of the time between this and the next admission she received methyl testosterone, 30 mg. daily.

In August, 1943 she developed auricular fibrillation. Her weight had increased 6 Kg. and a small amount of protein was now found in the urine. She was digitalized and the auricular fibrillation ceased. Perirenal air injections were repeated but failed to show an increase in the size of the adrenals. Because of gradually increasing polycythemia with hematocrit levels of 52 to 56 per cent, phlebotomies were carried out at various subsequent intervals. After discharge she was able to return to school for a very brief period.

In May, 1944 she was hospitalized again because of increasing upper abdominal pain. During this admission there was 2 plus albuminuria and a few red and white cells were found in the urinary sediment. Phenolsulphonphthalein excretion was 25 per cent and in thirty minutes, 50 per cent in two hours. Non-protein nitrogen ranged from 25 to 30 mg. per cent. Exploration of both suprarenal regions were performed by Drs. J. J. Morton and E. B. Mahoney. The adrenals were not enlarged and sections were interpreted by most observers as showing hyperplasia of the cortex. The ovaries and uterus were found to be very small.

After discharge in July she was given 30 mg. of methyl testosterone and 1 mg. of alpha-estradiol daily for about four months, and approximately every three months phlebotomy was performed which temporarily relieved the polycythemia and headache. However, the blood pressure remained around 200/130 and the weight gain continued.

When she was next admitted in April, 1945, her weight was 72 Kg. She was placed on the rice and raisin diet advocated by Kempner,[20] with a caloric intake of between 800 and 1,000 calories. During the first two months on this regimen she felt better than she had in some years and her blood pressure had decreased (150–170/100–100). During ninety days she

lost 17 Kg. Rather suddenly thereafter she became very weak, fainted several times and it was found that her serum proteins had dedecreased to 5.1 Gm. per cent from previous levels of 6.4 Gm. per cent to 7.1 Gm. per cent. The diet was changed to one liberal in proteins and low in calories and she was discharged in August. For two months thereafter she felt much improved and was able to visit relatives in the mid-west.

In November, 1945 she had frequent and prolonged epistaxes. She was markedly anemic and was found to have a urinary tract infection. A urea clearance was 50 per cent of normal on two occasions; blood non-protein nitrogen was 35 mg. per cent; the blood pressure was 205/120.

In February, 1946 she was admitted for treatment of the urinary tract infection with penicillin. The blood pressure was 205/140. In June it was necessary to admit her again because of epistaxes and from this time until her death her arms and legs were continually covered with bruises and ecchymoses.

In December, 1946 the blood pressure was 210–240/150 and a pulsus alternans was noted at times. Blood non-protein nitrogen was 37 mg. per cent, fasting blood sugar 76 mg. per cent and hematocrit 47 per cent. In March, 1947 she was brought in because of extreme dyspnea, insomnia, failing vision, epistaxis and back pain. Her face was fiery red and her stature shorter than before. She had advanced hypertensive retinopathy, cardiac hypertrophy, tachycardia, a gallop rhythm but no signs of congestive failure. The urine contained albumin, red cells, leukocytes and casts. The blood urea nitrogen was 50 mg. per cent and the glomerular filtration rate, determined by Dr. C. Waterhouse, was 17 ml. per minute. Treatment consisted of digitalization and a low salt, low protein diet. The blood pressure dropped slightly and she lost some weight. After two weeks she wished to return home and was discharged on this regimen.

Two weeks later she entered the Community Hospital, Warsaw, N. Y. and Dr. P. A. Burgeson was kind enough to furnish us with the following data: The blood non-protein nitrogen was 59 mg. per cent, serum calcium 8.5 mg. per cent and phosphorus 4 mg. per cent. A glucose tolerance test was as follows: Fasting specimen 95 mg. per cent, one-half hour 145 mg. per cent, one hour 165 mg. per cent, two hours 170 mg. per cent, three hours 150 mg. per cent. Radiographs of the skull showed expansion and deepening of the sella turcica with erosion of the posterior clinoid processes. Two weeks after admission the blood non-protein nitrogen had risen to 117 mg. per cent and one week thereafter, shortly before death, it was 168 mg. per cent. It was decided that the patient's death was due to renal failure and uremia.

An autopsy was performed by Dr. J. Tannenberg of the Genesee Laboratory, Batavia, N. Y. and we are indebted to him for the following information: "There was anatomical evidence of a chronic nephritis, hypertrophy of the left ventricle of the heart, a tumor in the posterior part of the pituitary gland with partial destruction of the back of the sella turcica, marked atrophy of the thyroid gland, some hypertrophy of the adrenals, marked atrophy, or better, hypoplasia of the ovaries and uterus."

BALANCE STUDIES

The patient was transferred to the metabolic unit on September 13, 1941, for the purpose of investigating the effect of androgens on her nitrogen, phosphorus, calcium and magnesium balances. These were followed continuously for 230 days, with the exception of three interruptions of two or four days, but never at a time when this interfered with the interpretation of results. She was placed on a basic diet which was thought to be adequate in its caloric content, to contain sufficient vitamins and to provide a liberal intake of protein and calcium. The same menu was eaten each day. Its composition was as follows:

	Estimated	Found by Analysis
Protein	100 Gm.	97.0 Gm.
Carbohydrate	154 Gm.	not done
Fat	56 Gm.	not done
Calcium	1.400 Gm.	1.035 Gm.
Phosphorus		1.480 Gm.
Calories	1,600 (approximately)	

The intake of nitrogen, calcium, magnesium and phosphorus was determined by the analysis of complete sample diets which were prepared from time to time during the course of the investigation. Since the

analyses exhibited no definite trend, the average values of the four elements mentioned were taken as the true intake in each period. It was possible to hold rigidly to this formula except in two periods, 6 and 11, when the carbohydrate intake was deliberately increased by 150 Gm. each day.

Observations were made over a total of forty-six five-day periods, the first six periods serving as controls. Androgen dosages are shown in Table 1 and Figures 2, 3 and 4. Certain deviations in dosage may be briefly mentioned at this point: In period 7 the 25 mg. dose of testosterone propionate was started on the second day, accounting for the total dose of only 100 mg. in this period. In period 15 one dose of 50 mg. was given on the first day and 10 mg. on each of the subsequent four days, making the total amount 90 mg. In the case of androsterone the daily dose was 25 mg. for the last four days of period 39 and the first four days of period 40. On the first and last days of this ten-day interval the dose was 12.5 mg.

Analytical Methods. Nitrogen in urine and feces was determined by the macro-Kjeldahl method, with determination of urinary nitrogen on twenty-four-hour specimens. Five-day aliquots of urine were pooled for the calcium, phosphorus and magnesium determinations. Stools were marked in five-day periods by the use of carmine. Calcium and magnesium were determined gravimetrically by the method of Washburn and Shear.[33] Phosphorus analyses were also carried out gravimetrically by the method of Epperson[10] and checked according to the Fiske-Subbarow[11] procedure.

RESULTS OF METABOLIC STUDIES

Nitrogen Balance (*Table* 1, *Fig.* 2). Maximum retention was achieved on an intramuscular dose of 25 mg. of testosterone propionate daily. Lowering the dose from 50 mg. to 10 mg. daily was soon followed by a sharp increase in urinary nitrogen, but the increase did not become great enough at the end of eight days to produce a negative nitrogen balance. Return to the previously high level of nitrogen retention did not occur when the 10 mg. dose was increased to 20 mg. Raising the dose from 20 to 50 mg. daily was followed again by definite nitrogen retention but at a lower level than had previously been noted with doses of 25 and 50 mg. The authors are not sure whether this last result was due to (1) some refractoriness on the part of the patient

TABLE 1

NITROGEN, CALCIUM, PHOSPHORUS AND MAGNESIUM BALANCES DURING THERAPY WITH ANDROGENS

Period No.	Nitrogen Balance Gm./ Period	Calcium Balance Gm./ Period	Phosphorus Balance Gm./ Period	Magnesium Balance Gm./ Period	Androgen mg./Period	Weight Kg.
1	+0.98	−1.322	−0.482	−0.096	None	53.01
2	−1.12	−1.380	−0.568	−0.119	None	52.87
3	−0.36	−1.402	−0.640	−0.180	None	52.18
4	−0.81	−1.350	−0.601	−0.133	None	52.45
5	−0.45	−1.227	−0.749	−0.089	None	52.35
6*	+6.68	−0.633	+0.537	−0.267	None	52.06
					Testosterone propionate	
7	+0.76	−1.315	−0.195	+0.066	100	53.62
8	+10.82	−1.146	+0.105	+0.019	125	53.15
9	+15.31	−0.515	+0.278	+0.052	125	53.55
10	+16.26	−0.533	+0.357	+0.099	125	54.16
11*	+21.98	−0.450	+1.260	+0.013	125	55.21
12	+14.13	−0.385	+0.423	−0.026	125	56.50
13	+16.59	−0.164	+0.486	+0.070	200	56.74
14	+13.89	−0.042	+0.485	−0.112	250	56.78
15	+11.84	−0.281	+0.461	+0.091	90	57.45
16	+3.90	−0.180	−0.213	−0.118	50	57.39
17	+2.13	−1.093	−0.235	+0.042	100	57.38
18	+1.38	−1.106	+0.199	+0.046	100	57.38
19	+2.10	−0.242	+0.270	−0.087	100	58.02
20	+2.19	−0.250	+0.135	−0.062	125	58.11
21	+7.47	+0.248	+0.464	−0.023	250	57.86
22	+9.57	+0.132	+0.508	−0.115	250	57.89
23	+8.38	+0.248	+0.343	−0.144	.....	58.43
24	−4.28	+0.105	−0.554	−0.099	.....	58.42
25	−14.72	−0.088	−1.056	−0.066	.....	57.74
26	−14.30	−0.148	−0.870	−0.021	.....	57.07
27	−10.77	−0.688	−1.097	−0.079	.....	57.40
28	−8.61	−0.716	−0.808	−0.054	.....	56.34
29	−9.14	−0.401	−0.704	0.000	.....	56.00
30	−8.12	−0.433	−0.384	+0.012	.....	55.88
31	−3.80	−0.718	−0.630	−0.018	.....	55.64
32	−5.65	−0.905	−0.760	−0.032	.....	55.48
33	−3.12	−1.245	−0.550	−0.052	.....	55.71
34	−2.08	−1.363	−0.454	−0.034	.....	55.52
35	−3.87	−0.986	−0.650	−0.030	.....	55.71
36	−0.95	−0.943	−0.529	−0.058	.....	55.55
					Androsterone	
37	−2.09	−0.825	−0.498	+0.032	62.5	56.09
38	−1.86	−0.850	−0.625	+0.018	62.5	56.11
39	−2.24	−0.980	−0.374	+0.018	112.5	56.26
40	−0.26	−0.953	−0.384	−0.019	112.5	56.09
					Dehydroisoandrosterone	
41	−0.13	−0.926	+0.811	−0.017	125	55.77
42	.....	−0.953	−0.722	+0.022	125	56.19
					Testosterone propionate	
43	−1.37	−1.083	−0.635	+0.067	125	56.89
44	+7.93	−1.056	−0.055	+0.012	125	56.93
45	+10.53	−0.806	−0.026	−0.041	125	57.25
46	+10.03	−0.855	−0.166	−0.053	125	57.97

* 150 Gm. of added carbohydrate given daily during these periods. Values are derived from actual analysis of diet, urine and feces. Each metabolic period is five days. Body weights recorded are under basal conditions on the first day of each period. Methods of analysis and intake given in text.

toward the hormone which had developed during the earlier administration of the 50 mg. dose or (2) whether she had arrived at a period when so much nitrogen had been retained that a diminishing effect was to be expected. After the hormone had been discontinued duration of the nitrogen-sparing action of the 50 mg. dose given in period 22 was exactly five days. Loss of previously stored nitrogen continued at a high level for thirty-five days after stopping the hormone and nitrogen equilibrium certainly was not attained even after sixty-five days. Neither androsterone nor dehydroisoandrosterone exerted any appreciable nitrogen-sparing effect when given what was believed to be an adequate trial in doses of 25 mg. daily intramuscularly. That the patient was again receptive to the 25 mg. dose of testosterone propionate is shown by her response in periods 43 to 46. An interesting response was noted in periods 6 and 11. In the former period no testosterone propionate had been given. Here the extra calories from carbohydrate had a small but definite nitrogen-sparing effect such as one might expect in a normal subject. Later (period 11), while the patient was under the full effects of a daily dose of 25 mg. of testosterone propionate intramuscularly, the same amount of extra carbohydrate was given again. It will be observed that the nitrogen-sparing effect of the added carbohydrate was superimposed upon that of the testosterone propionate. The extra sugar produced a mild glycosuria (7 to 8 Gm. per day), some apathy and moderate drowsiness. Net nitrogen retention after eighty days of testosterone propionate therapy was 159 Gm. Net loss of nitrogen during the seventy days in which the hormone was discontinued was 90 Gm. The balance, therefore, revealed a gain of 69 Gm. It appears evident that the initial storage of nitrogen was so great that considerable amounts of it must have been deposited, presumably in the muscles. While the initial loss of nitrogen was fairly rapid upon discontinuing treatment, about 43 per cent was still present in the tissues even after seventy days. The data also suggest that a much smaller dose of testosterone

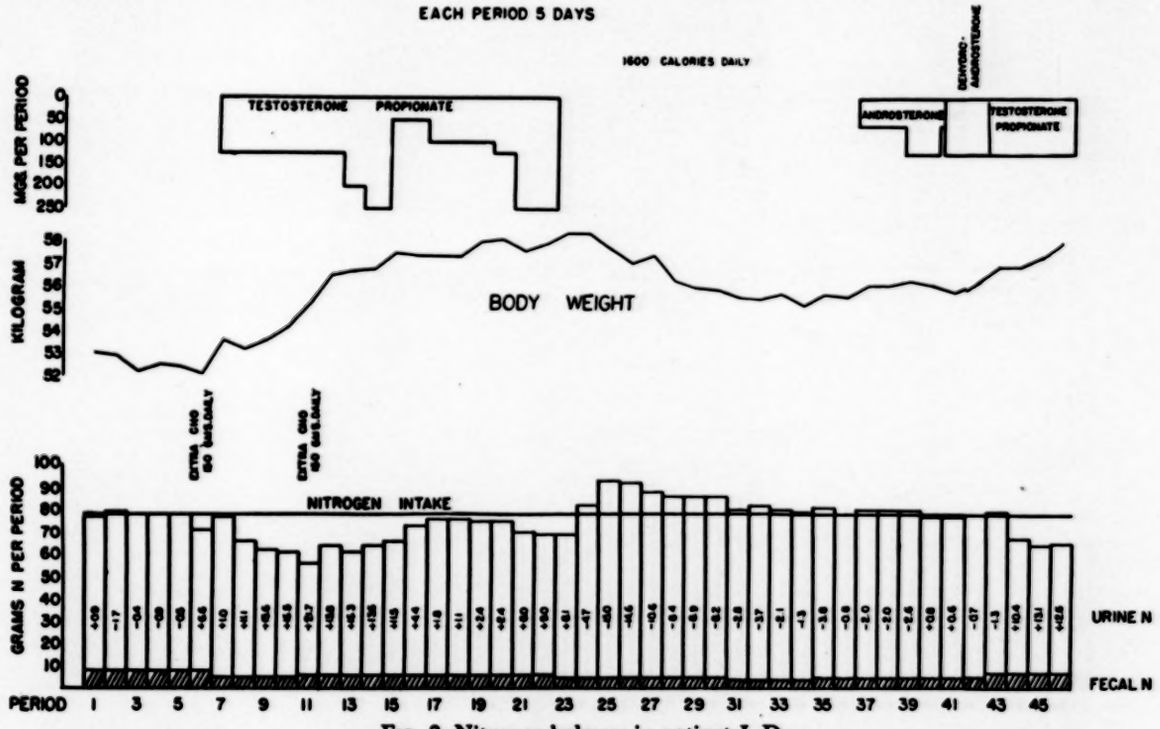

FIG. 2. Nitrogen balance in patient J. D.

propionate might suffice to enable a subject to retain nitrogen which had previously been deposited. (Periods 15 to 18.)

Creatine and Creatinine Excretion. During the six control periods the urine contained an average of 520 mg. of creatinine (range 437 to 584 mg.) and 720 mg. of creatine (range 630 to 810 mg.) daily. With the administration of testosterone propionate, the creatinine gradually increased to around 770 mg. daily. The creatine, however, did not decrease as it has in other individuals studied.[37] Nevertheless, when the injections were discontinued, the usual increase of creatinuria took place, amounting to over 1 gm. daily from the twentieth to the thirtieth days.

Calcium Balance (*Table* 1 *and Fig.* 3). Calcium loss from the skeleton was definite during the control periods. Unfortunately, it was necessary to keep the patient in bed because of her back pain; hence the negative balance was probably aggravated. As Howard et al.[16] have shown with convalescent fracture patients and Deitrick and Whedon[7] with healthy normal adults, immobilization in bed may lead to a marked increase of urinary calcium excretion.

The loss was gradually checked by testosterone propionate. During treatment the urinary calcium excretion diminished, and to a slight but definite degree fecal calcium was likewise decreased although no net retention of calcium was observed. A sudden increase of fecal calcium in period 18 is difficult to explain. The value obtained on analysis was higher than any during the entire investigation and may have been in error.

In period 6 when extra carbohydrate was given there was diminution of urinary calcium almost as great as the change with testosterone propionate. Hence the nitrogen-sparing effect previously discussed seems to have been accompanied by saving of calcium and, as will be seen later, phosphorus

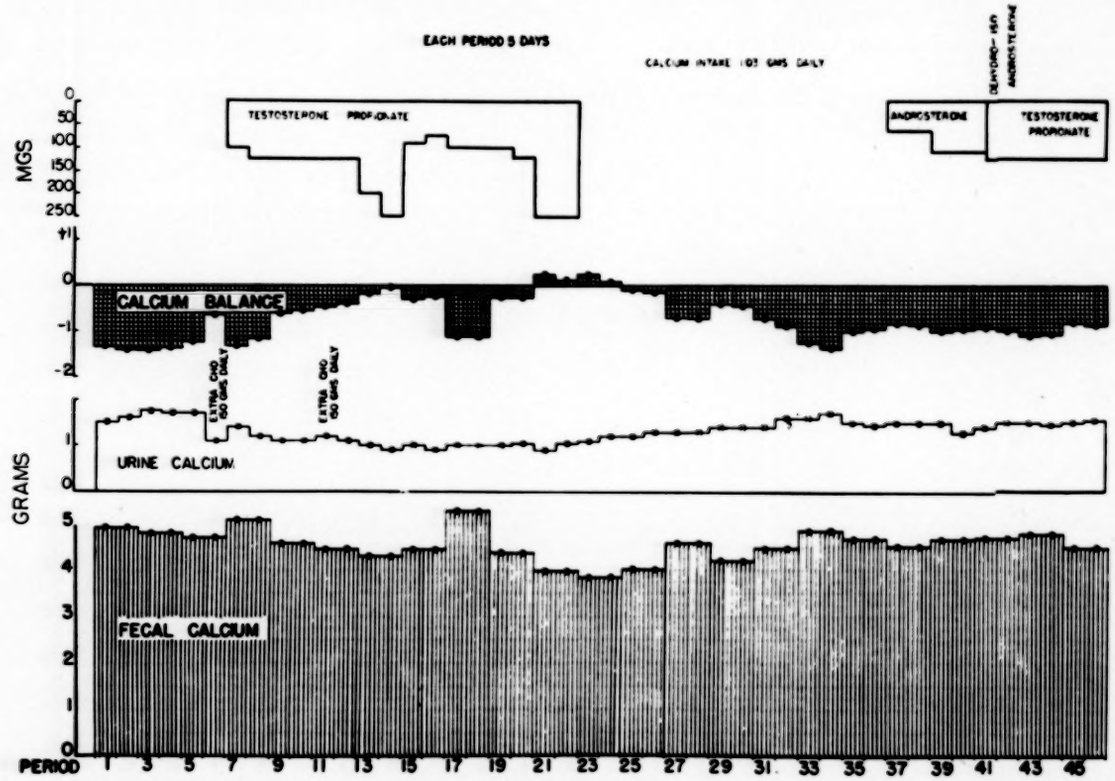

FIG. 3. Calcium balance in patient J. D. Values plotted represent Gm. and mg. per period, respectively. Because of difficulty in separation of stools into periods, the average value of two periods has been used in constructing the curve of excretion of fecal calcium. The high stool calcium in periods 17 and 18 are due to a high value in period 18.

as well. Furthermore, one may question whether the negative balance of calcium was exaggerated by an insufficient caloric intake. By the usual standard her dietary calories were presumed adequate in that she maintained her weight as well as a

of the theoretical phosphorus balance. As shown by Reifenstein et al.[26] it is possible to calculate a theoretical phosphorus balance if one knows the calcium and nitrogen balances, assuming that the calcium-phosphorus ratio of bone is 2.23 and the nitrogen-

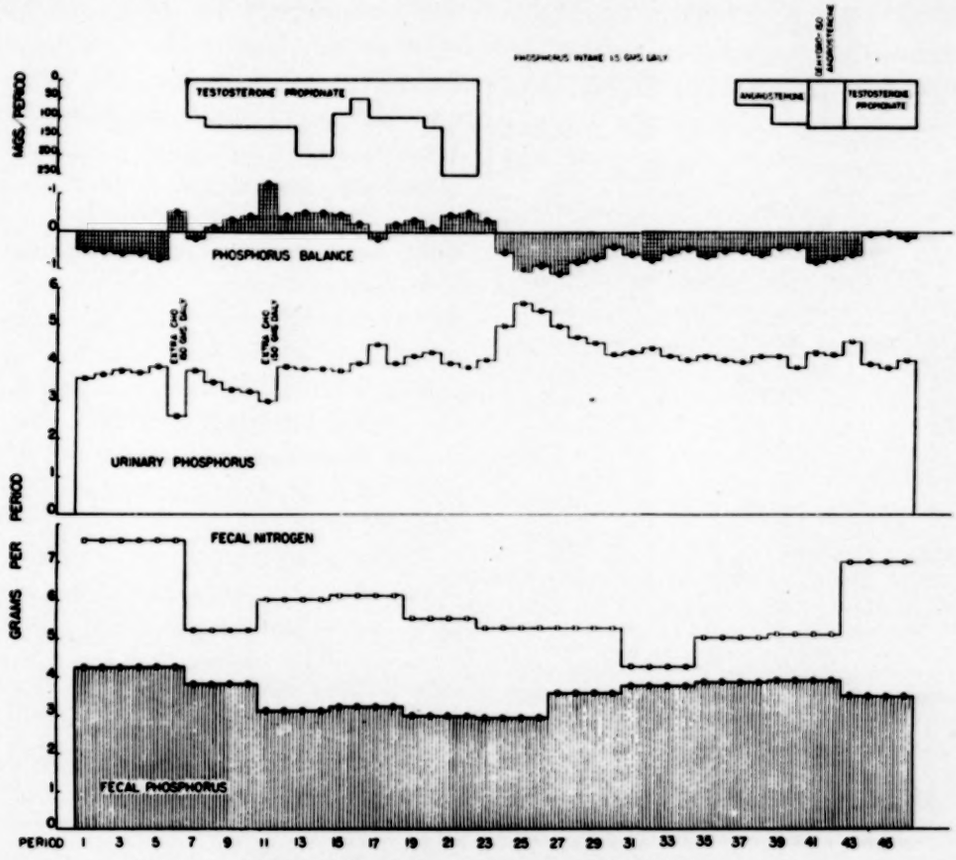

FIG. 4. Phosphorus balance on patient J. D.

fairly constant nitrogen equilibrium during the control periods.

Phosphorus Balance (*Table* 1, *Fig.* 4). Phosphorus excretion in the urine was not affected, but fecal phosphorus decreased in the periods of nitrogen retention and small net retentions of phosphorus were observed. After testosterone propionate was discontinued there was a sharp increase in urinary phosphorus with a gradual return of fecal phosphorus to higher levels. The depressant effect of extra carbohydrate on urinary phosphorus, as shown in period 6, appeared similar to the results obtained on nitrogen and calcium excretion.

The net retention of phosphorus was significant when checked by the calculation

phosphorus ratio of muscle is approximately 15. For example, during periods 7 to 22 when the patient was under testosterone propionate therapy, she retained 150.3 Gm. of nitrogen and lost 7.4 Gm. of calcium. Observed phosphorus retention was 4.8 Gm. To this must be added 3.3 Gm. of phosphorus which was made available from the calcium loss, making a total of 8.1 Gm. of phosphorus. The theoretical phosphorus retention, on the basis of 150 Gm. of nitrogen retained, is 10 Gm. so that the observed balance of phosphorus is in fair agreement with the theoretical.

Magnesium Balance (*Table* 1). Small amounts of magnesium were retained during periods of testosterone propionate ther-

apy mainly because of diminished fecal excretion of this substance.

Energy Metabolism. During the patient's residence in the metabolism unit periodic estimations were made of her basal metabolic rate, respiratory quotients and

TABLE II
ENERGY METABOLISM IN CUSHING'S SYNDROME

Period No.	Date	Testosterone Propionate, Total Additive Dose mg.	Basal Respiratory Quotient	Basal Calories /M²/Hr.	Basal Metabolism (Aub-Dubois)* %
3	10/24/41	0	0.765	25.3	−38.0
4	11/1/41	0	0.762	28.0	−31.5
5	11/7/41	0	0.775	26.9	−33.3
9	12/3/41	250	0.739	32.4	−20.5
11	12/16/41	575	0.801	32.6	−19.5
	(High carbohydrate diet—period No. 11)				
14	12/27/41	950	0.764	30.9	−22.5
16	1/8/42	1270	0.759	31.3	−23.0
20	1/30/42	1715	0.755	26.0	−33.0
25	2/25/42	2340	0.750	30.9	−23.0
34	4/10/42	None for 55 days	0.794	26.0	−33.0

* Determination of basal metabolic rate was carried out by use of the Tissot spirometer with subsequent gas analyses after the method of Haldane.

ability to utilize glucose. These observations were always begun fourteen hours after the previous evening meal. Expired air was collected in a Tissot spirometer for periods of ten minutes or more and analyses for oxygen and carbon dioxide were made with the Haldane apparatus.[8]

When glucose was given, the dose unless otherwise specified was 25 Gm. so that oral and intravenous administration could be compared. Sugar in the blood was determined by the method of Benedict,[25] that in the urine by the method of Hawkins and Van Slyke.[25]

Basal Metabolism. The consistently low basal metabolic rate was undoubtedly an expression of the deficient protein content of the body tissues. It will be noted (Table II) that a rise in the basal metabolic rate occurred during the intensive testosterone propionate therapy. Control levels were on the average minus 34 per cent while during treatment the rate rose to minus 21 per cent. In period 20, while the patient was still taking testosterone propionate, there appeared to be a fall to the pretreatment level. Whether this was due to a technical error could not be determined; on the other hand, similar fluctuations in basal metabolic rates under androgen therapy have been observed by others. Howard, Wilkins and Fleischman[17] treated sexually immature dwarfs with methyl testosterone and noted irregular, unexplained fluctuations in the basal metabolic rate. These were thought *not* to be due to the influence of the thyroid gland since the same results were obtained upon treating a cretin. Under hormone therapy our patient's blood cholesterol fell from over 260 mg. per cent in the control period to an average of 160 to 170 mg. per cent in period 16. By period 29 it had risen again to 280 mg. per cent.

Conclusions drawn from respiratory quotients are extremely hazardous when the data are obtained from individuals whose tissues deviate so far from the normal as in this patient. Aside from the fundamental disturbances in the handling of foodstuffs which we were trying to explore there was superimposed the condition of protein deficiency.

The basal respiratory quotients (Table II), were uniformly low[27] in spite of her slightly increased protein intake (about 1.8 Gm./Kg.). Even in period 11 when 150 Gm. of extra carbohydrate were given daily, the basal respiratory quotient was 0.801. Wells and Kendall,[34] Long[21] and Ingle and Thorn[18] thought the "sugar hormones" in some way interfere with carbohydrate oxidation. Thorn and co-workers[31] found that the respiratory quotient of some patients with Addison's disease was high and treatment with "sugar hormones" diminished these high values. The low respiratory quotient values of our patient, therefore, might be partially explained on the basis of defective carbohydrate oxidation. The finding that in acute experiments she was able to raise her respiratory quotient signifi-

cantly and oxidize considerable amounts of carbohydrate casts doubt on such a possibility.

Sugar Tolerance. Oral and intravenous sugar tolerance tests were done before and during testosterone therapy. While all the tests were not carried out for a uniform length of time, certain conclusions may be drawn from Figure 5. During the control periods the oral test showed a diabetic type of curve while during treatment with testosterone propionate the blood sugar level dropped more rapidly, being below control values by the third hour. Since the response to intravenous injection before and after treatment was practically the same, the insulin mechanism was probably not affected but improved absorption of glucose from the gastrointestinal tract is suggested.*

The respiratory quotient increased significantly after each dose of glucose (Fig. 5), indicating that considerable amounts of carbohydrate were being oxidized. This is shown more clearly in an experiment done 55 days after testosterone propionate therapy had been discontinued. (Table III.) In this experiment following the injection of glucose the non-protein respiratory quotient rose to 0.938. From the information in this table an estimate of the carbohydrate oxidized can be made but the amount deposited in liver and muscles is, of course, unknown. Of the 27.5 Gm. of glucose injected 9.5 Gm. were recovered from the urine. In the five hours she produced 89.4 calories from carbohydrate, i.e., 21.8 Gm. of glucose were oxidized. In other words, 3.8 Gm. over and above the glucose given were accounted for. Although it appears

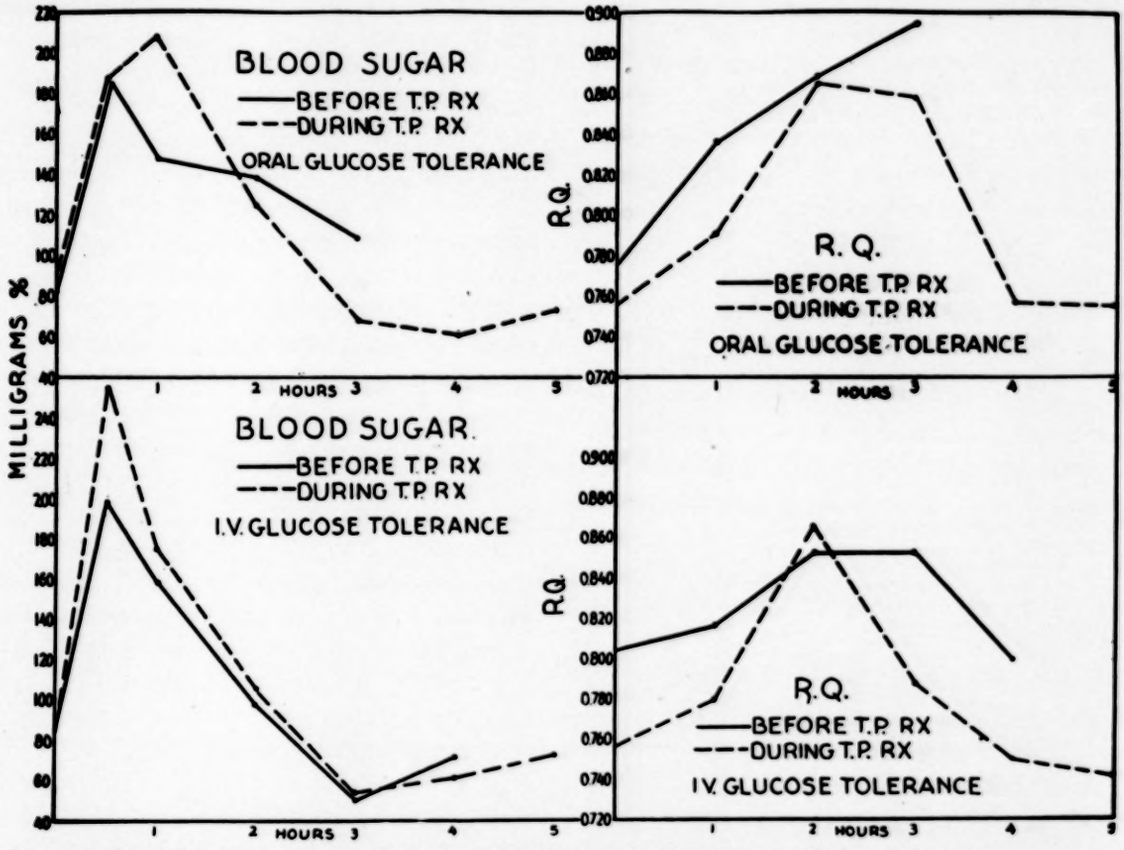

FIG. 5. Oral and intravenous glucose tolerance and respiratory quotients obtained before and during testosterone propionate therapy. T.P. = testosterone propionate; Rx = therapy.

* Freeman, Looney and Hoskins[13] found marked variation in glucose tolerance curves when duplicate determinations were made in normal individuals. However, the subjects were not on a constant diet.

that during the first hour after glucose both protein and fat were being spared, if one takes an average of the first two hours little if any protein appeared to have been spared by the carbohydrate but the oxidation of fat was decreased.

TABLE III
FIVE-HOUR CARBOHYDRATE BALANCE STUDY FOLLOWING INJECTION OF 0.5 GM. GLUCOSE/KG. OF BODY WEIGHT IN CASE OF CUSHING'S SYNDROME*

Time Hours	Urine N†	Urine Sugar	Blood Sugar	Non-protein R.Q.	Total Calories Derived from		
					Protein	Fat	CHO
	Gm	Gm	Mg %				
Fasting	0.278	0	55	0.783	7.4	22.8	8.1
½	.....	...	191				
1	0.216	6.3	105	0.885	5.7	13.2	23.8
2	0.394	3.2	62	0.938	10.5	6.0	25.2
3	0.355	...	56	0.893	9.4	10.3	18.9
4	0.291	0	...	0.789	7.7	24.2	10.3
5	0.253	0	66	0.799	6.7	22.5	11.2

* 27.5 Gm. of glucose injected during thirty minutes.
† Urine was obtained at hourly intervals by means of an indwelling catheter. Blood sugar was obtained immediately after the urine specimen on the average of fifteen minutes following release of the catheter clamp. (Following withdrawal of each urine specimen, the bladder was washed with sterile distilled water.)

After the patient had been on the low caloric rice diet of Kempner[20] for three months an oral glucose tolerance test gave the following results: Fasting blood sugar 65 mg. per cent, one-half hour after glucose 87 mg. per cent, one hour 92 mg. per cent and two hours 84 mg. per cent. This in no way resembled the former or subsequent diabetic type of curves. The change must have been due to the low caloric, high carbohydrate, low protein diet. It appears likely that either glycogen stores had been depleted or glyconeogenesis had decreased.

Neutral 17-ketosteroid Assays. Determinations of neutral 17-ketosteroid excretion were carried out for the first twenty-five periods in 1941 according to the method of Holtorff and Koch.[15] Control values averaged 19.1 mg. per twenty-four hours while under testosterone propionate therapy the patient excreted an average of 32 mg. per twenty-four hours. Since testosterone propionate is converted to and excreted as a 17-ketosteroid, the rise in androgen output under treatment was to be expected. Three and one-half years later further determinations were made when she was placed on the 1,000 calory rice and raisin reduction diet. The 17-ketosteroid values as determined by the modification of Talbot et al.[29] fell from a control level of about 30 mg. per day while she was on an average hospital diet to an average of 20 mg. per day after she had been on the low protein diet for over a month. The higher level of excretion during the control days of this time may have been due to the different method but more probably was associated with increased severity of the disease. The diminished excretion of androgen while she was on the diet was probably related to its extremely low protein content. Attempts to suppress adrenal function further with desoxycorticosterone acetate[28] were made at this time. Gradually increasing doses of 0.5 mg. to 2 mg. were given daily over a period of forty days. As feared the blood pressure increased and headaches were worse so that treatment was discontinued. No further reduction of neutral 17-ketosteroid excretion was observed. Substitution of progesterone[23] likewise had no effect.

COMMENTS

The hyperadrenocorticism in our patient was unquestionably due to basophilic hyperpituitarism with excessive production of adrenocorticotrophic hormone as originally postulated by Cushing.[5] It is unfortunate that roentgenologic evidence for this was not found until shortly before her death. Evidence of diminished pituitary activity as it is related to the gonads was revealed by amenorrhea and markedly decreased or even absent gonadotrophic hormone in the urine. The latter has also been reported by Albright[1] and Jores.[19]

It is the impression of the authors that in many respects the condition of this patient was improved to a considerable degree by treatment with testosterone propionate. Her general strength and well being were

greatly improved, and her mental outlook and spirits were better. She was up and about without too many complaints, was able to return to school, ride her bicycle and play outdoors; whereas before treatment her backache and abdominal pains were so severe that she was compelled to lie in bed most of the time and, indeed, for a period required immobilization on a Bradford frame. Surprisingly little masculinization was encountered despite the enormous amount of male hormone she received.

From the laboratory point of view nitrogen and phosphorus retention and diminished excretion of calcium were demonstrated. These confirm the observations of Albright et al.[1] Another beneficial effect may have been a more normal type of sugar tolerance curve.

In other respects the condition of our patient deteriorated even while under treatment. The hypertension became more severe, retinal arteriosclerosis increased, headaches were intensified and she developed auricular fibrillation. It is possible that the androgen contributed somewhat to these effects because of its electrolyte-retaining properties.

After intensive therapy was relaxed the unfavorable conditions which developed were related mainly to the osteoporosis, polycythemia, cardiovascular system and the kidneys. While it is possible that superimposed infection of the urinary tract hastened the onset of uremia, we believe that the intense vascular changes were responsible primarily for the gradual decrease of renal function and final uremic state.

Of more than passing interest was the temporary improvement which took place on the low caloric rice diet of Kempner[20] and which was accompanied by loss of weight, decrease of blood pressure, observation of a normal sugar tolerance curve and decrease of neutral urinary 17-ketosteroids. The latter decrease suggests lowered formation of certain steroids as a result of decreased precursors in the diet, and it is unfortunate that we were not able to obtain information on the excretion of urinary corticoids at this time.

The sudden appearance of generalized muscular weakness, fainting spells and decrease of serum proteins suggests that the depletion of protein from the tissues had been seriously aggravated by the diet. One wonders whether this could have been prevented by the simultaneous administration of testosterone propionate. Such a combination of therapeutic measures deserves a trial although the possibility of spontaneous remissions must be borne in mind.[3,5,30]

SUMMARY

Clinical and metabolic observations are presented in a case of Cushing's syndrome studied continuously for 485 days and followed closely for five and one-half years.

Treatment with testosterone propionate* intramuscularly produced the following effects:

1. Retention of nitrogen. The maximum effect was achieved with 25 mg. daily. The data also suggest that a much smaller dose of androgen might suffice to hold in the body nitrogen which had previously been deposited at a high level of dosage. When added carbohydrate was given, its nitrogen-sparing effect was superimposed on the effect of the testosterone propionate. Seventy days after treatment had been discontinued over 40 per cent of the deposited nitrogen was still retained by the body.
2. Retention of phosphorus.
3. Diminished calcium loss from the body.
4. Retention of magnesium.
5. A rise of the basal metabolic rate toward but not to the normal level.
6. Possibly better absorption of glucose from the gastrointestinal tract with resulting improved sugar tolerance.
7. Clinically, there was improvement of those symptoms associated with calcium loss

* The endocrine products used in these studies were furnished by Ciba Pharmaceutical Products, Inc., Summit, N. J.

from the skeleton and with protein depletion of tissues (osteoporosis, pain, strength, "well being"). Symptoms and signs relating to the vascular system were not improved but progressed while under treatment.

The patient was able to oxidize considerable amounts of carbohydrate. The implications of this with regard to the theory that the "sugar hormones" oppose peripheral oxidation of carbohydrate is discussed.

For a brief period she improved while on a low protein, low caloric, low salt diet. After several months this produced severe weakness.

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Insulin Mixtures and Conservation of Insulin*

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My colleagues and I have had almost ten years of experience with insulin mixtures, starting shortly after Lawrence and Archer[1] and Graham[2] had announced that they were finding mixtures helpful. Our early results were not entirely satisfying, but procedure for adjusting dosages has improved over the years and we now are obtaining reasonable control of glycosuria with only one injection daily in a fair majority of cases of what we call grade 4 diabetes, that is, cases in which the diabetes is of such severity that the total daily insulin requirement of the patient exceeds 30 units.[3–7]

We have not used mixtures prepared by the manufacturer. Failure to do so is because of uncertainty regarding the stability of such preparations.[8] Also we have not attempted the preparation of mixtures in the insulin vial although this has been proposed by some physicians. Instead we have instructed our assistants and patients to make the mixture in the syringe according to the technic herein described. The procedure has the disadvantage of being somewhat difficult to teach to patients and for that reason it is unsuitable for the very ignorant or for those who are handicapped by poor vision. For such individuals we resort to other methods of insulin administration. In most cases, however, the patient has been able to acquire the technic of making mixtures and the advantages of the procedure are important. They are: (1) that in a large proportion of all cases adequate control of glycosuria is obtainable with a single injection daily; (2) that continued insulin action is assured over the night with little danger of reaction in the night and (3) that the total daily unitage of insulin required is usually somewhat smaller than the unitage necessary for comparable control of glycosuria when dependence must be placed either on soluble insulin or on protamine zinc insulin used alone.

Another very great advantage of insulin mixtures prepared in the syringe is that, being tailor-made, each component of the mixture can be adjusted to fit the needs of the individual. Requirements differ with different patients. Some need a mixture with more quick action; others one with more retarded action. Also in our experience the requirements of the individual are likely to change from time to time. By using mixtures the amount of each type of insulin can be fitted to the individual and later can be altered to meet his changing requirement. In the majority of cases, two parts of soluble insulin added to one part of protamine zinc insulin best fits the needs most of the time. This is a ratio of 2 of soluble insulin to 1 of protamine zinc insulin. In other cases other ratios have been advantageous. The appropriate ratio rarely exceeds 3:1 or falls below 1:1. A ratio lower than 1:1 usually implies that protamine zinc insulin alone will do all that is required. As was shown by Colwell and his colleagues[9,10] when the ratio is less than 1:1, the amount of regular insulin contained in the mixture is largely bound by the excess of protamine present in the protamine zinc insulin. It thereby is converted into insulin with retarded action. The action of an insulin mixture in which the ratio exceeds 1:1 is intermediate between the quick action of soluble insulin and the retarded action of protamine zinc insulin. The action of such mixtures may be monophasic as Colwell has maintained; nevertheless, some rapid action provides for the elevated insulin requirement provoked

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by the taking of food during the day and enough slow or retarded action persists to provide for the diminished but continuing requirement for insulin in the fasting hours of the night.

Protamine insulin was developed by Hagedorn and his colleagues[11] between 1934 and 1935. Its stabilization and additional prolongation of action by addition of zinc soon followed, and protamine zinc insulin became available commercially in January, 1937. The action of this product was sufficiently prolonged to permit control of diabetes over the night when only one injection was given the preceding morning. It also provided for some overlap from one twenty-four hour period to the next, an insulin insurance from one day to the next as Joslin[12] aptly termed it.

The characteristics of the new insulin gave rise to the hope that its use alone would permit control of glycosuria with only one injection daily, but this hope soon had to be abandoned. In cases of mild diabetes, that is, cases in which a total daily dose of not more than 20 units is required, the condition can be handled safely by the use of only protamine zinc insulin, but in cases of severe diabetes a dose sufficient to prevent gross glycosuria after meals commonly precipitates an insulin reaction in the night. Night is a bad time for a reaction because the patient and his family are asleep. Furthermore, the hypoglycemia which develops from an overdose of protamine zinc insulin comes on so gradually as to be almost symptomless, and the patient may remain quite unaware that his blood sugar has fallen to unphysiologic levels. This may go on unrecognized for weeks or months or even for years. The problem may be further complicated in some patients by what Bowcock[13] called "paradoxical glycosuria." In these instances, without symptoms being provoked, the blood sugar according to Bowcock's hypothesis, when it reaches certain low levels, trips the mechanism which releases sugar from the liver and the amount of sugar thus released exceeds what can be utilized immediately. Glycosuria then occurs and the patient in consequence is led to increase still more the already excessive dose of insulin until finally he is taking a sufficient unitage to precipitate a dangerous reaction.

An extreme example of postponement of ill effects of unappreciated overdosage with protamine zinc insulin came to my attention very recently. The patient, a man forty years of age, had been using protamine zinc insulin for ten years, taking a single dose daily. He had noted no ill effects although the occasional appearance of sugar in his urine had led him to gradual increase of his dosage until for several years he had taken 100 units every day. Then suddenly and without much warning he suffered from a severe convulsion with loss of consciousness and hemiplegia. Fortunately the hemiplegia was transitory. In other instances permanent cerebral damage has resulted from such overdoses.

In the case which I have mentioned the patient apparently was able to tolerate an excessive dose of insulin for many years. This is unusual. As a rule vague but unpleasant symptoms develop fairly early even when the patient experiences none of the symptoms which commonly are attributed to insulin reaction, symptoms such as sweating, anxiety, tremor and diplopia, with later loss of consciousness and convulsions. A fair proportion of diabetic patients who come to the Mayo Clinic using protamine zinc insulin complain on arrival of headaches, backaches and leg aches, associated with feelings of exhaustion and weakness with an incapacity for mental concentration; their symptoms disappear soon after the dose of insulin has been lowered. In a few instances actual mental deterioration has been evident and then recovery has been delayed.

The symptoms mentioned also are observed in patients who use mixtures of soluble and protamine zinc insulin, especially when the amount of protamine zinc insulin is large. Therefore, when the total insulin requirement is large, involving the use of more than 20 units of protamine zinc insulin combined with 40 units of soluble insulin, we now advise either increasing

only the amount of soluble insulin in the mixture or abandoning the attempt to obtain control of glycosuria with a single injection daily and giving a supplementary dose of soluble insulin before the evening meal.

Control of glycosuria in some instances is less satisfactory with mixed insulins than we should like to have it. In certain cases results superior to those obtainable with mixed insulins are to be had with injections of soluble insulin given three or four times daily or with protamine zinc insulin and soluble insulin administered in separate sites. In a very few cases of severe diabetes best control has resulted from giving soluble insulin before breakfast and globin insulin before the midday meal. The action of globin insulin seems not to extend much beyond the sixteenth hour. However, with two injections a day, one of soluble and one of globin insulin, this difficulty is overcome. We have had relatively little experience with globin insulin and none with histone insulin. The latter is made with protamine obtained from the thymus and, like protamine insulin, is turbid. Bailey and Marble[14] showed that its action parallels closely that of protamine zinc insulin although its activity is slightly less prolonged.

DIRECTIONS FOR USE OF INSULIN MIXTURES

Filling the Syringe. As Sprague[6,7] has emphasized use of extemporaneous mixtures of protamin zinc insulin and soluble insulin in one syringe calls for precaution to prevent introduction of one kind of insulin into the other vial. An appropriate volume of air is first injected into the vial of protamine zinc insulin and the needle is withdrawn without any insulin being permitted to enter the syringe. Then the desired dose of soluble insulin is drawn into the syringe in the usual manner. After this the needle is again inserted into the vial of protamine zinc insulin, and the desired dose is allowed to flow into the syringe and to overlie the soluble insulin which is there already. The two insulins are then mixed by drawing a small bubble of air into the syringe, inverting the syringe several times and then expelling the bubble.

Adjusting the Dose of Insulin. By adjustment of the size of each component of the insulin mixture more or less of either slow or quick insulin action is obtainable. This adjustment cannot be rigidly prescribed although usually some variation of the plan outlined in subsequent paragraphs proves satisfactory.

Two urine tests a day are necessary, one before the morning meal, the other before the evening meal. The urine should be freshly secreted; that is, the bladder should be emptied approximately thirty minutes before collection of the specimen for examination. In the early treatment of a patient tests are made four times daily; that is, before each of the three principal meals and at bedtime. Later two, three or four tests daily are secured, depending on the severity of the diabetes and the desired precision of control. Usually with diabetes of moderate severity adequate information is obtainable by testing twice daily, before breakfast and before supper.

Sugar in the urine before the morning meal calls for more protamine zinc insulin (more late action) whereas sugar in the urine before the evening meal demands more soluble insulin (more early action).

When a change is to be made from use, either of protamine zinc insulin alone or of multiple doses of soluble insulin, a safe initial dose of the mixture is two-thirds of the total daily units taken recently. The ratio at the start is 2:1; that is, 2 units of soluble insulin for each unit of protamine zinc insulin. However, if the patient has been using a very large unitage of protamine zinc insulin, something less than two-thirds of the recent dosage is desirable because of the holdover of the effect of the large preceding dose of protamine zinc insulin. For example, if a patient has been taking 60 units of protamine zinc insulin, I should give no insulin at all for twenty-four hours and then begin with approximately two-thirds of 60, which would be approximately 40 units of a mixture with a 2:1 ratio; for example, 28 units of soluble and 14 units of protamine zinc insulin. Rarely should the initial dose exceed 60 units, and

in the absence of evident acidosis increases of dosage should be made cautiously during the first few days of treatment. The full effects of the starting dose may not be apparent for several days.

Later adjustments are made as follows: When the test of the morning urine has been grade III or IV* for three or four mornings in succession the protamine zinc insulin compound of the mixture is increased by 2, perhaps by 4 units. However, if this necessitates giving more than 20 units of protamine zinc insulin, the attempt is made to obtain control by increasing the soluble insulin component of the mixture; and if this provokes an insulin reaction during the day, by giving instead a small dose of soluble insulin before the evening meal. Likewise, when the test of the morning urine has been 0 for several successive days, usually not more than three, the protamine zinc insulin component is reduced in size by 2, perhaps 4 units. For traces of sugar in the morning urine (tests grade I or II) no change is made. The presence of a trace of sugar in the morning provides a measure of assurance that the dose of protamine zinc insulin has not been excessive.

When the test of the urine before the evening meal has been grade III or IV for two or at most three successive days, the soluble insulin component of the mixture is increased by from 2 to perhaps 4 units. This change is made on the following morning. Likewise, when the test of the urine before the evening meal has been 0 for two or more successive days, the soluble insulin component is reduced by 2 or perhaps 4 units.

In most cases when reasonable control of glycosuria has been effected, it is inadvisable to make changes in the doses of the two kinds of insulin more frequently than has been suggested. Factors other than insulin, notably emotional disturbances and variations of food intake, may be responsible for transient glycosuria. On the other hand, the occurrence of a *bona fide* insulin reaction usually calls for lowering the next day's dose of insulin. When the reaction has developed between breakfast and supper, the soluble component of the mixture should be lowered the following morning. If it has developed in the night, the protamine zinc insulin component should be lowered. The magnitude of the changes made in the insulin dosage depends, as a rule, on the size of the total daily unitage of insulin. When this is less than 40 units, changes in steps of only 2 units are advisable. When it is more than 40 units, changes in steps of 4 units are desirable. Some patients, particularly children, are so sensitive to small changes that alterations of 2 units at a time are sufficient irrespective of the size of the total daily dosage.

Use of Insulin in Emergencies. A single morning dose of insulin, even a mixture of insulins, will rarely provide adequate control of diabetes in emergencies. Many infectious diseases intensify the diabetic state. They seem to provoke a degree of insulin resistance so that larger and more frequently administered doses of insulin are required. Likewise, after serious injuries, especially those involving fractures of the bones, and after operations additional insulin is usually required.

Considerable advantage attends continued use of some protamine zinc insulin in emergencies. Although multiple injections of soluble insulin are also made, prolonged action of the protamine zinc insulin is helpful to insure a continuous insulin effect day and night. When the patient has been maintained either with one injection daily of protamine zinc insulin alone or with a mixture of soluble insulin and protamine zinc insulin, the dose of protamine zinc insulin or that of the mixture is continued as before, with additional injections of soluble insulin made at intervals. Freshly secreted urine is tested for sugar every three hours. It also is tested for diacetic acid whenever the test for sugar is grade IV. For a grade IV test 10 units of soluble insulin is administered. With young children, 6 units may suffice. However, if the test for diacetic acid is positive in a

* The grade IV test with Benedict's qualitative solution is represented by red, grade III by yellow, grades I and II by green turbidities. Essentially the same colored turbidities are obtained with the clinitest.

urine that tests grade IV for sugar, adults are given 12 or more units of soluble insulin and children 8 or more units.

With protamine zinc insulin given in the morning, it may not be necessary to test the urine or to administer additional soluble insulin between 10 P.M. and 6 A.M. The severity of the condition determines this. When the emergency has passed and convalescence has begun, the requirement for insulin may decline rather quickly and the supplementary doses of insulin must be diminished. When recovery is complete, the dose of insulin that was effective before the emergency will usually again suffice.

CONSERVATION OF INSULIN

I should like to emphasize a point already made: that use of insulin mixtures properly adjusted has frequently effected a saving of insulin, in that the unitage required for reasonable control of glycosuria has been less in many cases than what had previously been employed. I also wish to emphasize that great saving in the use of insulin can be accomplished by not using insulin at all, except in periods of emergency, with diabetic patients who are grossly overweight. The treatment of choice for the obese diabetic patient is a reducing diet, not insulin. When such a patient is given a diet as low or lower in calories than his basal caloric needs, he usually becomes aglycosuric without insulin and the giving of insulin may only stimulate his appetite and add to his desire to eat beyond his diet. Also when the body weight of such a patient has been lowered to the standard weight for height, a maintenance diet usually can be tolerated without insulin.

When I add the saving of insulin effected by these two means, the resulting conservation of insulin in regard to our patients is impressive. Thus, among one hundred consecutive new diabetic patients using insulin on arrival and treated as ambulants in the Mayo Clinic, sixteen were obese. These sixteen overweight people had been using a total of 307 units of insulin daily and on their dismissal were using only 80 units. The remaining patients, numbering eighty-four, had been consuming a total of 2,636 units of insulin every day and on dismissal had lowered their daily consumption to 1,843 units. The total daily unitage for the one hundred patients was 2,943 before arrival and 1,923 on dismissal. This represents an average saving for each patient of about 10 units daily, and a total annual conservation of 372,300 units, or almost one thousand vials of U-40 insulin every year. However, more important is the fact that this conservation of insulin was accompanied by improvement in control of the patients' diabetes.

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A Liberal Regimen of Treatment of Diabetes

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In the preinsulin era regulation of the diet was the only means of treating the patient with diabetes. The intake of food always had to be reduced; the amount of deprivation depended on the individual patient's supply of endogenous insulin. This meant considerable hardship for the severe diabetic but there was nothing else to be done. The patient was subjected to a rigid course of dietary instruction which he had to follow if he wished to survive.

With the coming of insulin, diets for diabetics gradually became more liberal and eventually were virtually normal. The insulin dosage was adjusted to a particular diet so that the patient's blood sugar level throughout the day was reasonably controlled. Diets used by different physicians varied considerably, from the low and moderate caloric diets to relatively high caloric diets; from low carbohydrate intake to a very high—sometimes unreasonably high—carbohydrate intake. We learned as time went on that generally a patient on a diet with 200 Gm. of carbohydrate and a reasonable caloric intake got along better than one taking only 100 Gm. of carbohydrate and the same number of calories. This fact was of value to the physician and of inestimable comfort to the patient to whom it meant that "life was again worth living."

Looking backward we can see that many queer things were done during this period. For instance, the diet was divided into three equal parts for each of the meals. The average individual ordinarily does not eat that way. Many people are accustomed to taking a breakfast consisting of half a grapefruit, toast and coffee. Suddenly if they become diabetic they had to eat a big breakfast because it was prescribed while they were in the hospital. Some acquired the habit of eating a big breakfast and learned to like it. Others did not enjoy it and never could adjust to this change in their life routine and gradually returned to their old habits.

Was this drastic change in a patient's dietary habits necessary? I never could see any sense to it. If a patient received 20-10-20 units of insulin a day with a heavy breakfast, the dosage could be changed to 10-10-20 if, with a light breakfast, the patient had a reaction during the morning. Now when a patient takes only protamine zinc insulin in the morning, it is even more essential that he eat a light breakfast for PZI does not begin to work until about noon. Hence during the morning the patient is unprotected and by noon the blood sugar may rise considerably. To prevent this post-breakfast rise when a patient takes a heavy breakfast some insulin is given with the PZI in the morning dose in the same syringe and all in one injection. The amount of insulin necessary can be adjusted quite closely after a few blood sugar checks are done at noon.

The point I wish to emphasize is that experience has taught us that forcing a diabetic patient into an artificial and distasteful routine is like trying to fit a square peg into a round hole and it is not a sensible procedure. The more closely we adhere to his normal living habits the easier the routine is for the patient and the better his cooperation.

Beside this an adverse psychologic factor is introduced by the very word "diet." Question any normal individual, examine him, discover about how much food he has been consuming daily for the past ten years (most people eat much the same from day to day unless they are obese) and then say: "My dear man, I will have to put you on a

diet now which you will have to follow closely." The estimate of what he has been eating for the past ten years will be, let us say, 2,000 calories a day. Now the diet is outlined, these things for breakfast, these for lunch and these for dinner. In doing this let us suppose that instead of giving him a 2,000 calory diet he receives 3,000 calories, that is, 50 per cent more than he has been taking. From the day he starts on the diet, even though it is 50 per cent more food, he will feel starved and that he is being deprived. He is not being deprived of food at all but only of his freedom to choose his food. This tremendous psychologic factor has not received the consideration it deserves in the treatment of diabetic patients.

The importance of this psychologic factor was well brought out during the war when thirty-six conscientious objectors volunteered as guinea pigs for experiments in human starvation at the University of Minnesota Laboratory of Physiological Hygiene.[1] These volunteers were prepared for semistarvation by three months of good eating, with an average of 3,492 calories daily. Then for six months they received two carefully rationed meals a day, totaling 1,570 calories. A daily sample was: pancakes, syrup, apple sauce, cornbread and jam in the morning; potato soup, stew and potatoes in the evening. Their psychologic reactions were most interesting. Although they knew that nobody would try to shove them aside, the hungry men began taking great care to guard their places on the chow line. They showed a strongly possessive attitude toward their food; at the table some leaned suspiciously over their trays "protecting" their rations with their arms. These men were "cultured and refined," the researchers reported, but soon they all unashamedly licked their dishes. (I have observed the same behavior in diabetic children who were on relatively high diets.) As they became more and more hungry food became the chief subject of their conversation and of their day-dreams. They became fond of poring over cook books and hotel menus. (Diabetics show the same tendency.) Some of the men started to replan their lives and talked of becoming cooks or farmers. They grew increasingly irritable and joked less and less. Eventually they grew too apathetic to bother with shaving, brushing their teeth or combing their hair. Their interest in study gradually collapsed but they felt closely identified with their group and with the starving throughout the world. They occasionally had "spells of elation, sometimes bordering on ecstasy," or were unduly depressed and discouraged. After six months of hunger they required six months to return to normal. During the first three months of rehabilitation their bad table manners and study habits showed little improvement; some men actually became more depressed and irritable than during semistarvation. As the effects of starvation wore off each man lost his sense of close identity with the group and began worrying about his own personal plans for a normal future.

Such a study as this is most revealing and presents food for thought in its relation to the treatment of diabetes. In managing diabetics we do not give diets as low as 1,570 calories but of 1,800 calories or more. However, it must be remembered that even on a 2,000 calory diet, a "planned diet," if the patient's diabetes is not well controlled he is not utilizing all the food and may be losing as much as 240 to 400 calories which are excreted as sugar in the urine. Such a patient, therefore, is actually starved. And even if he is losing but 80 to 100 calories in this manner, which is quite common, there is still the psychologic factor of the "straight jacket" which the patient cannot and does not escape, try as he may. This is something which we must seriously take into consideration.

Sporadic attempts have been made in various parts of the world to manage diabetic patients on "free diets." This is the opposite extreme from the usual practice. There has been some value in these attempts for they have shown that if a patient who has been on a calculated diet is placed on a free diet he will at first "eat his head off"

but finally settles down to a fairly regular routine which will not vary much from day to day. The weakness in this idea is that good therapeutic control of these patients, that is of their glycemic level, was not insisted upon with appropriate adjustment of the insulin dosage. They were allowed to carry on with excessive hyperglycemia. It was assumed that it was impossible to adjust the insulin closely enough to control their diabetic state so little was done and little was accomplished. In this country Tolstoi[2] has used such free diets without adequate control and in a few decades we shall know the results.

The question confronting medical men treating diabetes is: Can the work with free diets be carried on successfully? Can the patient on such a liberal diet be adequately protected? If adequate protection can be furnished, such a regimen should be beneficial to patients. If it cannot, the procedure should be condemned regardless of the patient's adverse reaction to dieting.

A little over a year ago I was confronted with a serious problem. Owing to overcrowding of our hospitals, some of my patients had to wait four to eight weeks for admission. This, of course, was an intolerable situation for once the diagnosis of diabetes has been made the patient's routine should be started immediately.

The difficulty of obtaining beds in the hospital and also the desire to see what could be accomplished in the management of diabetes outside a hospital stimulated the present research. The questions to be answered were: Is it possible to solve the individual problem of the diabetic in the office without sending the patient to the hospital where all things are controlled? Can the insulin dosage be adjusted closely so that the patient is well protected? Can this be done without teaching him the elaborate methods of calculating diets? This questioning presented a real challenge. If proper control of the patient could be accomplished with only slight regulation of his eating habits, the adverse psychologic factor connected with dieting would be eliminated.

The policy I inaugurated was to inquire about the patient's eating habits to see whether there was any gross abuse of food. Most persons have fairly well fixed eating habits. They eat much the same kind and quantity of food, day in and day out. The only directions I gave them were as follows: Omit all sugar, pastry and soft drinks. Eat everything else as you always have but avoid stuffing. Do not eat more than two slices of bread with each meal and if you have potatoes eat only one slice of bread. You may have ice cream without any syrup over it once a week but no soft drinks. The rest of the time use fresh fruit, fruit canned without sugar or cheese and crackers for dessert. This seemed to all patients a very simple directive, one they could easily follow. There was no planning, no weighing or measuring of food. This represented only a slight change from what they had been doing in the past decade or more and thus there was no feeling of going on any rigid dietary routine, no feeling of being in a "straight jacket."

In evaluating these instructions one must remember that a diet of 200 Gm. of carbohydrate, 100 Gm. of protein, 100 Gm. of fat, with a total of 2,100 calories, is in fact a normal diet. A patient who eats in a normal fashion, with the slight restrictions mentioned, will not consume any more food. In fact, I believe from the evidence so far that most patients consume less and are happy about the fact that they do not have to be on a "strict diet."

In establishing the routine the patient comes to the office the first day and the blood sugar and urine are examined three times, before breakfast, lunch and dinner, with the patient taking food according to his regular habits. Usually all three blood sugar levels are quite high in which case I administer 20 units of protamine zinc insulin after the evening check-up and advise the patient to come to the office each subsequent morning at 8 A.M. without breakfast. Each morning the fasting blood sugar is

checked and the patient is given 20 units of PZI. The fasting blood sugar yields definite information on the fall of the blood sugar for if the PZI dosage is adequate the fasting blood sugar will be normal. If it is normal, the dose should not be increased for the patient will encounter an insulin reaction. If it stays elevated, the dosage should be increased by 5 units until the fasting blood sugar falls to normal; the patient is kept on that dosage provided there are no insulin reactions. If reactions occur the dosage is reduced by 5 units. Each day the patient is instructed about insulin administration so that by the time his routine is adjusted and the blood sugar in the morning remains normal he knows how to administer the insulin and is on his own.

The next point to determine is whether the blood sugar remains normal throughout the day, that is, before breakfast, lunch and dinner. Sometimes as soon as the fasting blood sugar level is adjusted, usually a week or two later, the blood and urine are checked three times daily before meals. It is ideal if all three blood sugar determinations are normal. If the morning and evening blood sugars are normal and the noon determination elevated, this is still satisfactory for such a patient does not have hyperglycemia more than 25 to 30 per cent of the twenty-four hours. Even a normal individual has a postprandial hyperglycemia, sometimes lasting two hours after each meal, or six hours a day. This is 25 per cent of the twenty-four-hour period and I use this as the standard for comparison in establishing the regimen of the diabetic.

If the morning blood sugar is normal and the noon and evening blood sugar elevated, this calls for additional units of regular insulin in the morning to prevent the postprandial rise of blood sugar following breakfast. This automatically reduces the evening blood sugar level as well. If the fasting blood sugar is above normal, this, of course, calls for an increase in the PZI dosage.

The results of this routine have been quite favorable for almost all the patients have progressed satisfactorily, with minimal loss of time and disorganization of their lives. The accompanying charts show seventeen patients who have had the longest follow-up. These were unselected, consecutive cases (although the order on the charts is not strictly chronological), showing their course after the preliminary period of adjustment at the office. On the charts this period is marked "daily checks." On Sundays the PZI was omitted as the dates at the top of the charts indicate. Hence the blood sugar usually rose on the following day.

CASE REPORTS

CASE I. A woman, aged sixty-four, was first seen on July 25, 1947, because of glycosuria. The three blood sugars before each meal were 217-282-316, with heavy glycosuria throughout, a faint trace of albumin and acetone 2+. (Fig. 1.) She was 15 per cent overweight and had been as much as 22 per cent overweight. There was no diabetes in the family. The blood pressure was 200 systolic and 100 diastolic. The blood sugar came down to normal on the third day (she had 25 units of PZI the first evening) and stayed at a normal level during twelve days of administration of insulin in the office, with the exception of August 4th following a Sunday on which insulin was omitted. At the end of this period all three blood sugars were normal and all insulin was discontinued. The next check-up, twenty days later, showed that all three blood sugar determinations were normal as did all subsequent checks.

One might say that this elderly woman might have been adjusted without insulin, but with a low diet it could not have been done so quickly nor with the same comfort to the patient. Also there is the psychologic advantage that having had insulin once even though her blood sugar has remained normal for eight months she knows that if she is careless she would have to go back to taking insulin. No patient wants this if it can be avoided.

CASE II. A Negro woman, aged fifty-two, had been losing weight and glycosuria had been discovered ten days previously after a bad cold. She was drinking much water and had polyuria and nocturia. Her mother and paternal uncle were diabetic. She was 19 per cent overweight and had been 31 per cent overweight. The blood pressure was 150 systolic and 80 diastolic.

On January 15, 1947, the three blood sugar determinations were 234-467-508, with a heavy glycosuria throughout and an albumin of 1+. (Fig. 1.) The first evening I gave her 15 units of insulin and 20 units of PZI and the following mornings 20 to 25 units of PZI. The blood sugar fluctuated somewhat and the fasting blood sugar was not normal until the twenty-second day. A recheck two weeks later showed satisfactory levels of blood sugar, 105-176-91. She was then taking 25 units of PZI which was reduced to 15 units. She has not been seen since.

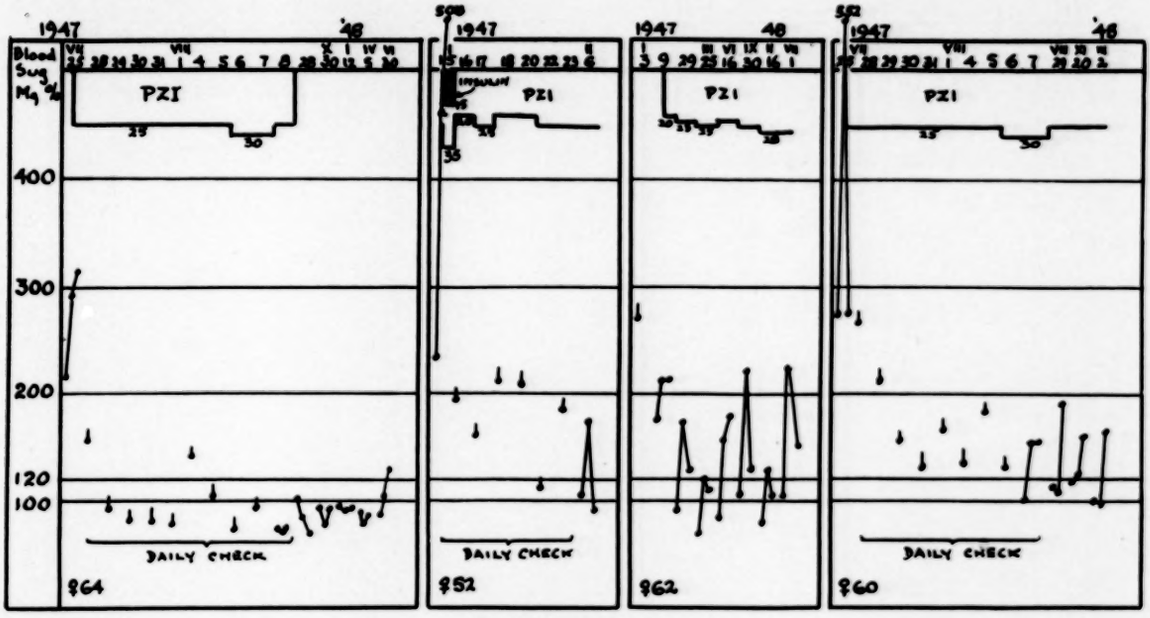

FIG. 1. Cases I to IV.

CASE III. A nurse, aged sixty-two, had had symptoms of diabetes for a month. A fasting blood sugar taken elsewhere was 271 mg. per cent, with the urine showing 4+ sugar. She was placed on a diet; she lost weight and the glycosuria disappeared. When I saw her on January 9, 1947, the glycosuria had reappeared. (Fig. 1.) She was 1 per cent underweight but had been 17 per cent overweight previously. A maternal cousin was diabetic. The blood sugars were 175-213-214, with heavy glycosuria throughout the day; no albuminuria was present. Since she was a nurse, it was not necessary to have her come to the office daily so I directed her to take 15 units of PZI each morning and to increase this by 2 units each subsequent morning until she encountered a reaction at which time she was to reduce the dosage by 2 units. I saw her a week later when the blood sugars were 91-174-130, with only a slight glycosuria at noon and in the evening on a dosage of 23 units of PZI. Subsequent PZI dosage has fluctuated between 22 and 28 units and subsequent check-ups have shown a good control for a year. It is obvious that she needs insulin despite her age. At the last examination on February 16, 1948, the three blood sugar determinations were 79-130-107.

CASE IV. A woman, aged sixty, reported that diabetes had been discovered four years previously. On a restricted diet glycosuria disappeared but symptoms of diabetes reappeared following an attack of influenza. She was 7 per cent overweight and had been 23 per cent overweight. There was no diabetes in her family. The blood pressure was 226 systolic and 120 diastolic. On July 25, 1947, the blood sugars were 272-552-275, with heavy glycosuria throughout, albumin 1+ and no acetone (Fig. 1.) She was given 25 units of PZI that same evening and each subsequent morning she received 25 units of PZI for nine days, with the fasting blood sugar dropping slowly toward normal. On the last day at the office the three blood sugars were 100-98-155, with only a trace of glycosuria in the evening. Her PZI was then reduced to 25 units upon which she continues. Subsequent checks have shown quite good control for eight months.

CASE V. This chart (Fig. 2) shows an interesting record over a period of twenty-five years. In 1923 when this patient was thirty-six years

old she came to see the author because of glycosuria. Her fasting blood sugar was checked; this was normal and there was no glycosuria. A glucose tolerance test the next morning showed a prediabetic curve, with the blood sugar not reaching normal for three hours and a quarter. and had been 24 per cent overweight. The blood pressure was 118 systolic and 90 diastolic. There was no diabetes in her family. The patient had five children and had not been ill except for colds.

All three blood sugar levels were quite high.

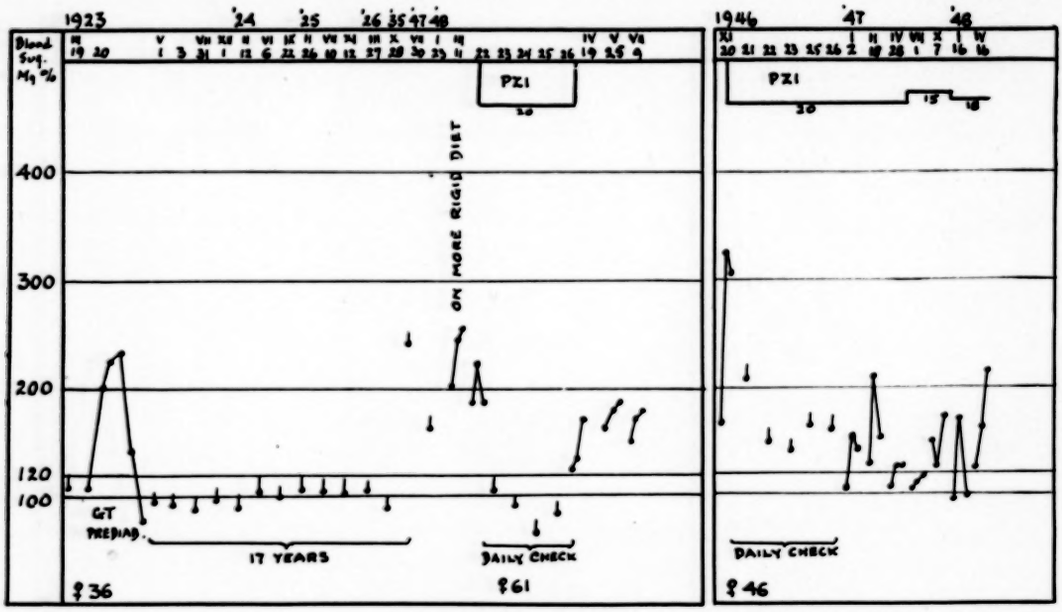

FIG. 2. Cases V and VI.

Afterward she watched her diet somewhat and a fasting blood sugar was determined periodically for twelve years. All these determinations were normal and glycosuria appeared but once during this period. The question in such a case is whether the patient will eventually become diabetic. Twenty-four years after she had first shown a prediabetic type of glucose tolerance curve, in 1947 and 1948, she had two more blood sugar tests taken elsewhere. Both of these showed elevation. When she came to see the author on March 11, 1948, the check-up showed blood sugars of 202-241-254, with no glycosuria in the morning but 2+ at noon and in the evening. The next day the blood sugar levels were 187-232-185. Twenty units of PZI were administered that evening. The blood sugar dropped promptly to normal the next morning and stayed normal the next four days at which point the PZI was discontinued. She is now sixty-one years old and the insulinogenic weakness revealed twenty-five years ago has come to the foreground in frank diabetes.

CASE VI. A woman, aged forty-six, had classical symptoms of diabetes. The discovery of glycosuria had been made one week before I saw her. She was then 12 per cent overweight (Fig. 2.) I gave her 20 units of PZI the first evening and beginning the next morning she received 20 units of PZI with a blood sugar check at noon each day for six days. After that she took 20 units of PZI each morning at home and the blood sugar level came down to normal throughout the day in the fifth month. It stayed at normal for three months after which there was a slight rise which did not become significant until April, 1948 at which time the dosage of 18 units of PZI was increased to 20 units.

CASE VII. A man, aged sixty-three, had glycosuria discovered nearly a year earlier. He had been on a 1,500 calory diet and became sugar-free but he had lost much weight and was feeling depressed. He had nocturia, three times during the night. He was 14 per cent overweight and had been 55 per cent overweight. His blood pressure was 140 systolic and 80 diastolic. There was no diabetes in his family. The glucose tolerance test on April 30, 1940, was performed before I saw him and showed a frank diabetic curve. The fasting blood sugar on May 14th was 187 mg. per cent. When he came to me, he was taking 40 units of PZI and on June 21st the blood sugar levels were 100-143-130, with no glycosuria. (Fig. 3.) The dosage

was reduced to 30 units of PZI, later to 28 units, and the subsequent checks all showed good control. During this time he was on an ordinary diet of his own choosing. On October 25th all insulin was discontinued but a check thirteen days later showed a considerable rise of the blood sugar so he was again placed on PZI, with a prompt response. All insulin was again discontinued eight months later. Since then, with the exception of a small dose of 10 units for a week in December, 1946, he has had no insulin and the diabetes has been well controlled even though he has been somewhat careless with his diet. His weight has increased from 180 pounds to 221 pounds and he has led a normal life in every way.

Although this patient is an elderly man, at the outset neither a low diet nor diet plus insulin controlled the diabetes adequately. Systematic check of the blood sugar three times a day yielded definite information as to how much insulin was required. When the diabetes had been controlled for a time, the insulin could be completely discontinued.

CASE VIII. Glycosuria had been found in a woman, aged fifty-one, a few days before she consulted me and she had had classic symptoms of diabetes for two weeks. She was 7 per cent overweight and had been 14 per cent overweight. The blood pressure was 146 systolic and 90 diastolic. There was no history of diabetes in her family. On her first check-up on October 29, 1947, the blood sugar levels were 167-250-184, with heavy glycosuria throughout; no albumin or acetone were present. (Fig. 3.) She was on a low diet at first but there was no response. Hence on December 1, 1947, she was started on the regular office routine with administration of PZI and the blood sugar dropped promptly to normal. After nine days all insulin was discontinued. A check-up a week later showed some elevation of the blood sugar and 20 units of PZI were administered that evening only. No insulin has been given since and her condition has remained in perfect control.

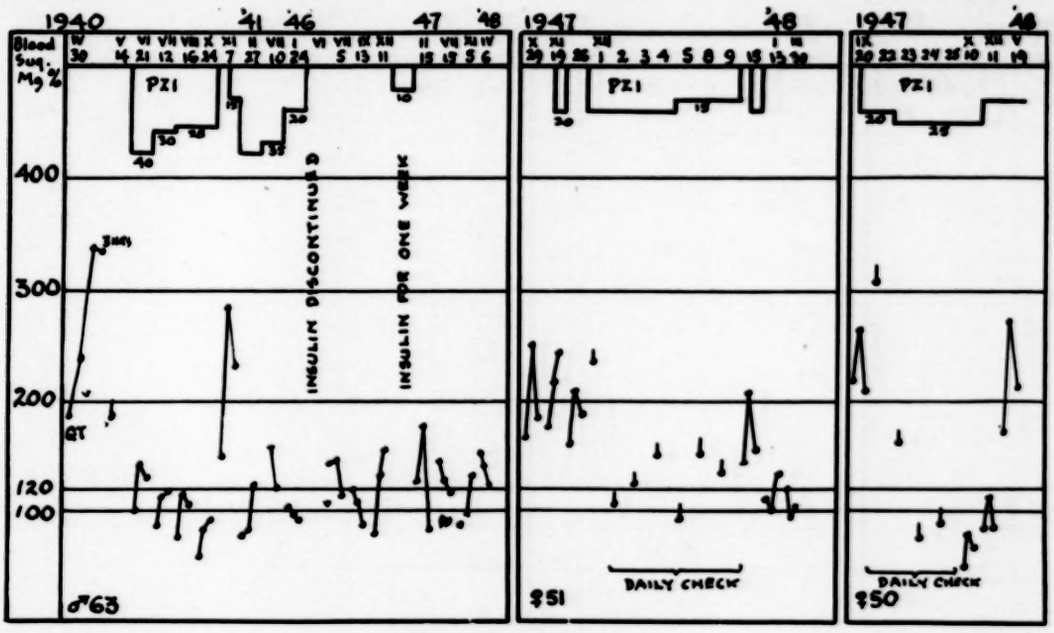

FIG. 3. Cases VII to IX.

CASE IX. A woman, aged 50, had had diabetic symptoms for several weeks and glycosuria had been discovered a few days previously. She was 12 per cent underweight and had never been overweight. The blood pressure was 112 systolic and 76 diastolic. There was no diabetes in her family. She had had two thyroidectomies in the past. On September 20, 1947, the blood sugar determinations were 219-263-210, with heavy glycosuria throughout; no albumin and acetone 3+ were present. (Fig. 3.) The PZI routine was started immediately and with the exception of the following morning the blood sugar level dropped promptly and stayed down throughout the day as shown by subsequent checks. The follow-up in the office lasted only four days. She is now taking 15 units of PZI daily.

CASE X. A woman, aged fifty-six, had been placed on a reduced diet because she had had glycosuria, and a fasting blood sugar a week

before I saw her was reported as 289 mg. per cent. On May 23, 1947, she was 24 per cent overweight and had been 36 per cent overweight. A maternal cousin was known to be diabetic. The blood pressure was 160 systolic and 100 diastolic. She had had virus pneumonia three years earlier. The blood sugars were 210-184-197, with heavy glycosuria throughout on the reduced diet. (Fig. 4.) The first evening she was given 15 units of PZI. This was increased to 20 and later to 25 units; the blood sugar level did not fall to normal for two weeks. The office routine was continued for twenty-two days, but the results as judged by subsequent checks were quite gratifying on a continually reduced dosage of PZI.

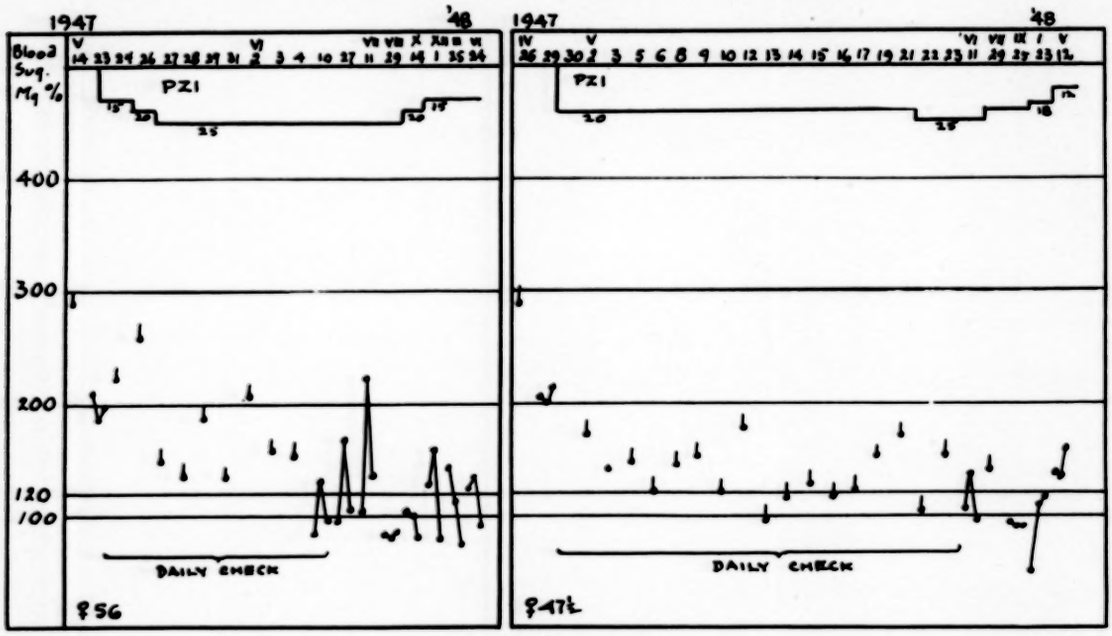

FIG. 4. Cases X and XI.

CASE XI. A woman, aged forty-seven, had been excessively thirsty for six months and glycosuria was found, with a fasting blood sugar level of 289 mg. per cent. There was no diabetes in her family. She had had a hysterectomy twenty-five years previously. She was 10 per cent overweight and had been 26 per cent overweight. The blood pressure was 190 systolic and 110 diastolic. On April 29, 1947, the blood sugar determinations were 206-202-214, with heavy glycosuria throughout, no albumin and a faint trace of acetone. (Fig. 4.) The office routine was started the following day with 20 units of PZI. This was continued for twenty-four days before the blood sugar level became normal on 25 units of PZI daily. Subsequent checks have shown normal blood sugars and she is now on 18 units of PZI; at the last examination this was reduced to 12 units. This patient could manage now without insulin except for the fact that she is quite careless about her diet and drinks considerably.

CASE XII. A woman, aged sixty-five, consulted the author because of recent glycosuria. Her mother, sister and brother were diabetic. She was 5 per cent underweight and her highest weight had been only 4 per cent above normal. Her blood pressure was 180 systolic and 96 diastolic. The first examination made on August 7, 1947, (Fig. 5) showed the following values for the blood sugar: 164-303-285; the urine sugar was 0, 1+ and 3+. Twenty units of PZI were administered that evening; then the PZI was increased to 30 units and the blood sugar dropped promptly so that after six days all insulin was discontinued. Subsequent checks have been normal.

CASE XIII. Glycosuria had been found eight months previously in a man aged thirty-four. On April 17, 1947, he was 22 per cent overweight and had been 36 per cent overweight. There was no diabetes in his family. The blood pressure was 134 systolic and 90 diastolic. The blood sugar levels were 117-147-230, and the urine showed a faint trace, 0 and 2+ sugar, with heavy albuminuria. (Fig. 5.) He was given 20 units of PZI the first evening and the two subsequent mornings. Three weeks later, on

20 units of PZI, the three blood sugars were normal and remained normal for four months. About that time he began to drink considerable quantities of beer and the next two examinations showed the result. His weight increased by 25 pounds. After this demonstration he is now

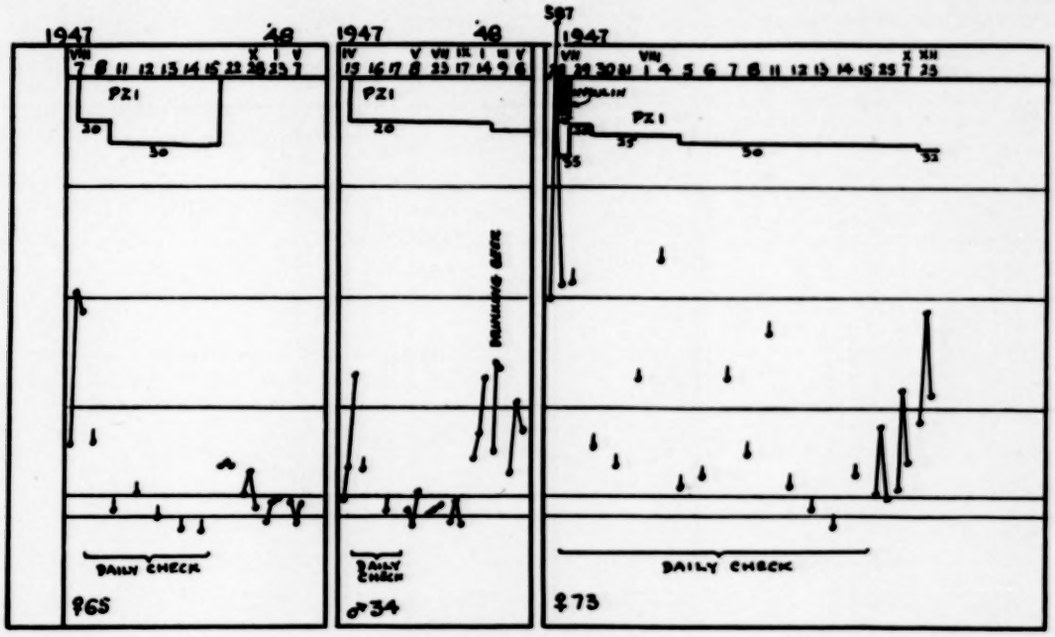

FIG. 5. Cases XII to XIV.

taking no beer and subsequent check-ups should show the result.

CASE XIV. A woman, aged seventy-three, had had glycosuria seven years previously with classic symptoms of diabetes. On July 28, 1947, she consulted the author because she again had been having nocturia and had lost weight. She was 14 per cent overweight and had been 45 per cent overweight. Her father and sister were diabetic. Her blood pressure was 144 systolic and 80 diastolic. The first check-up showed the blood sugar levels to be 300-587-313. The urine showed heavy glycosuria throughout; no albumin and acetone of 1+. That evening she received 15 units of insulin and 20 units of PZI and then started the office routine which was continued for fourteen days at which time the fasting blood sugar was normal. A check-up ten days later showed good control. Five weeks later the blood sugars were somewhat elevated but not seriously for her age. However three months later, on 32 units of PZI she was definitely out of control and the dosage was increased to 36 units.

CASE XV. A woman, aged twenty-eight, consulted me because of glycosuria which had been discovered a few days before on a routine examination. She had been thirsty for a month and had been losing weight. She was 4 per cent underweight and had never been more than 3 per cent overweight. A paternal cousin was a diabetic. Her blood pressure was 110 systolic and 70 diastolic. The first check-up on November 17, 1947, showed blood sugars of 192-258-340, with heavy glycosuria throughout, no albumin and a trace of acetone. (Fig. 6.) She received 20 units of PZI that evening and 20 units of PZI each morning for seven days. The blood sugar came down promptly. The first recheck, a week after the daily examinations in the mornings, showed a slight elevation of blood sugar without any PZI that morning and so she received a dose that evening. However, after that single dose all PZI was discontinued for two weeks when a recheck showed the same slight elevation of the three blood sugars. Another trial with PZI was made and nearly three weeks later there was greater elevation of the three blood sugars and as a result she resumed taking 20 units of PZI each morning.

CASE XVI. A man, aged sixty-three, had glycosuria which had been discovered three weeks earlier. There was no familial history of diabetes. He was 15 per cent overweight and had been 29 per cent overweight. The blood pressure was 162 systolic and 106 diastolic. The first check-up on January 20, 1948, (Fig. 6) showed blood sugars of 306-275-250, with heavy

glycosuria throughout, a faint trace of albumin and no acetone. Twenty units of PZI were given that evening and later 25 units of PZI each morning for the next ten days. He continued taking 25 units of PZI each morning and on March 10th all three blood sugars were normal and he is continuing on the same routine.

done in the past, thus upsetting his mental equilibrium and creating needless psychologic problems. If the patient is allowed to regulate his own restrictions, all that is necessary is adjusting the insulin dosage to that routine and the patient will be happy. When a "fixed routine" is imposed on him,

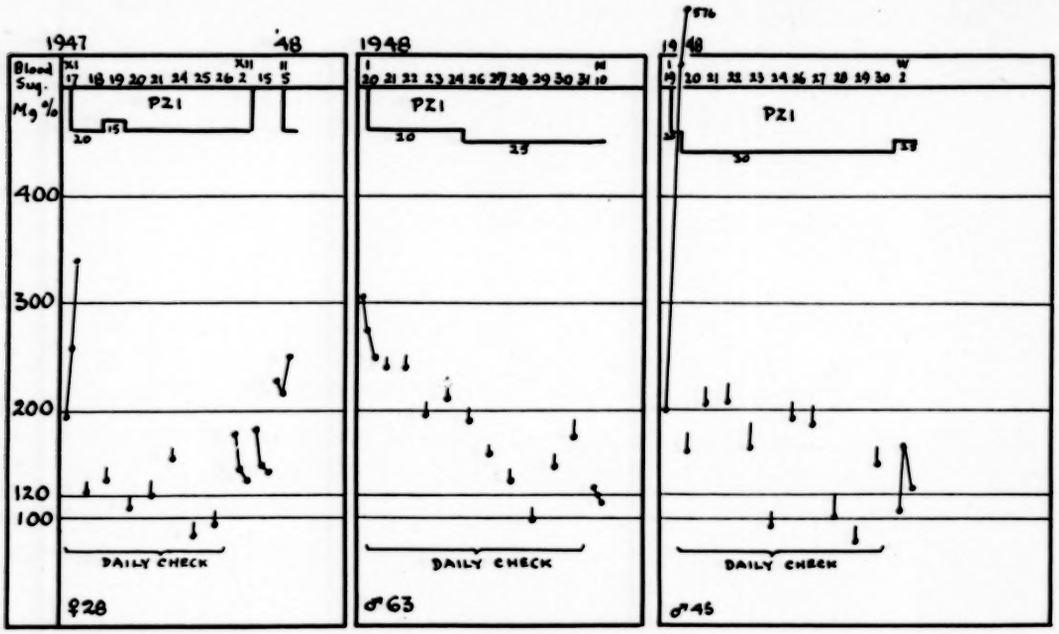

FIG. 6. Cases XV to XVII.

CASE XVII. A man, aged forty-five, had known of glycosuria for two months. There was no history of diabetes in his family. He was 14 per cent underweight but had been 30 per cent overweight. The blood pressure was 116 systolic and 70 diastolic. On January 19, 1948, the blood sugars were 201-522-576, with heavy glycosuria throughout, a trace of albumin and no acetone. (Fig. 6.) After the usual evening dose of 20 units of PZI he received 30 units of PZI each morning for the next ten days. A check-up two months later, on 25 units of PZI, showed virtually normal blood sugar levels with glycosuria persisting. He is now continuing on 20 units of PZI.

SUMMARY AND CONCLUSIONS

A study of the progress of a group of patients shows that a diabetic can live on a practically normal diet such as he has been accustomed to all his life with only a few proscriptions. There is no need for completely reorganizing his life, as has been

additional problems are created and the patient is not happy. It matters little if the difference between a fixed routine and the elective routine is from 100 to 300 calories since whatever the voluntary choice of food by the patient the insulin is adjusted to care for it.

I am not advocating a "free diet" and "careless control" but an almost free diet with adequate control as reflected in the blood sugar level throughout the day, not merely in the fasting blood sugar. If the fasting blood sugar is normal, the noon sugar elevated and the evening blood sugar normal, this is acceptable. If the fasting blood sugar is normal and the noon and evening levels high, some insulin should be added to the PZI in the morning to take care of this postprandial rise. If all three blood sugars are elevated, the PZI should be increased and the subsequent check up will show whether or not some insulin should be added to the PZI. Both insulins

should be given in the same syringe, in one injection, so as to diminish the discomfort. It does not matter whether some of the insulin is changed over to PZI. The important thing is not "how much of the insulin is changed over" but "how it works." Only in this way can the patient's individual problem be solved satisfactorily.

With such a regimen the patient loses no time from work. By losing no time he also loses no income. The cost of his treatment is also greatly reduced and he is not overburdened with impractical details which disturb his equanimity. His problem is reduced to the absolute minimum and the burden of it rests largely in the hands of the physician guiding him. Furthermore, this regimen relieves pressure on hospital beds which today are needed more urgently for other types of cases.

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Fatal Anuria, the Nephrotic Syndrome and Glomerular Nephritis as Sequels of the Dermatitis of Poison Oak*

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THE dermatitis of poison oak (Rhus toxicodendron diversilobum) is generally considered to be an annoying but benign episode. When mentioned at all by patients, it is not often accorded the dignity of a place in the physician's notes. This is particularly true when these notes describe the details of graver illness appearing more recently than the dermatitis. Such refusal to take the disorder seriously may account, at least in part, for inability to find modern reports of complications following poison oak dermatitis; the older literature contained an occasional but inadequately documented report of death.

There are at least two reasons for expecting that complications might arise after the dermatitis of poison oak. Obviously, the broken skin could serve as portal of entry for infection with all of its potentialities in production of disease. Secondly, and apparently less well known, the provocative agent is one which causes sensitization.

In view of current conceptions of the parts played by infection and sensitization as etiologic factors in nephritis and periarteritis nodosa, it may be of interest to record some instances in which renal complications appeared in several patients as the dermatitis of poison oak was healing. In one there was fatal anuria with severe degeneration of renal tubules. In four the nephrotic syndrome was prominent; pure lipoid nephrosis seemed a likely diagnosis in three of these, chronic glomerulonephritis in one. In two additional cases, with suspected and probable streptococcal infection, the syndromes resembled the onset of glomerular nephritis; there was considerable tubular degeneration in one of these. Still another patient has been observed in whom the features of the initial stage of glomerular nephritis followed the dermatitis of poison oak; in this case the diagnosis was thought to be periarteritis nodosa and the report will be presented elsewhere[1] together with a verified case of periarteritis nodosa following the closely related primrose dermatitis.

CASE REPORTS

CASE 1. Mr. L. P. (E33251), a wood-pattern maker fifty-four years of age, entered Stanford University Hospital in uremia on June 30, 1943.

One daughter was highly susceptible to the dermatitis of poison oak, but not so the wife and another daughter. The mother, father and a sister died of cancer.

He had suffered many severe bouts of poison oak acquired on slight exposure. Because of one attack in 1942 he took to bed for two weeks. A routine life insurance examination was successfully passed within the previous ten years. There had been no exposure to heavy metals and he had taken no medicines. His health generally had been good.

While in Sierra Nevada on May 30, 1943, he gathered and carried wood which smoked badly when burned; he was also exposed to the smoke. He soon had severe dermatitis, with vesicles on face and neck by June 3rd, when the eyelids were swollen (without eruption or irritation on the lids). A cough producing about 15 cc. of greenish-yellow sputum daily began on June 7th, and on the following day he was nauseous, vomited and went to bed. On June 9th a physician found moderate edema of the

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face and ankles and on the neck a very slight dermatitis which soon disappeared. The cough improved but the legs ached. Thiamin and unidentified medicines for the skin were given, but not sulfonamides. About this time the urine became scant but not smoky or bloody, and it was found to contain many casts and much protein but few erythrocytes. There was an anuria for a day on June 15th when arterial pressure and a blood count were normal and the concentration of urea in the blood was 54 mg./100 cc. Nausea and vomiting increased, oliguria continued and he entered the hospital after a day or two of rapidly progressing dyspnea.

He was very ill and semi-comatose, lying flat and with deep, rapid respiration. Nutriture and development were good. There was no fever. The optic fundi were normal; the eyelids were slightly puffy and the buccal mucosae were dry. The jugular veins were not distended. The heart was enlarged only slightly or not at all and was regular at a rate of 70. The sounds were normal, without gallop, rub or murmur; the second sound was louder at the pulmonic area than at the aortic area. The lungs were clear. The abdomen was entirely negative. The back of the trunk was normal. Arterial pressure was 130/90 mm. Hg. There was a very slight trace of ankle edema, and a few small, almost healed patches of dermatitis were found on the neck.

The concentration of hemoglobin was 16.8 Gm./100 cc., and there were 5,370,000 erythrocytes and 7,100 leukocytes per cu. mm.; 90 per cent were polymorphonuclear neutrophiles, 7 per cent lymphocytes, and no eosinophiles were counted. Urine for twenty-four hours measured only 160 cc. and contained 7.2 Gm. of protein, 20,000,000 casts (none of red blood cells, 20 per cent waxy and granular, and 80 per cent broad), 10,000,000 erythrocytes, and 50,000,000 leukocytes and renal tubular epithelial cells of which 5,000,000 were oval fat bodies. Concentration of urea in the blood was 455 mg./100 cc.

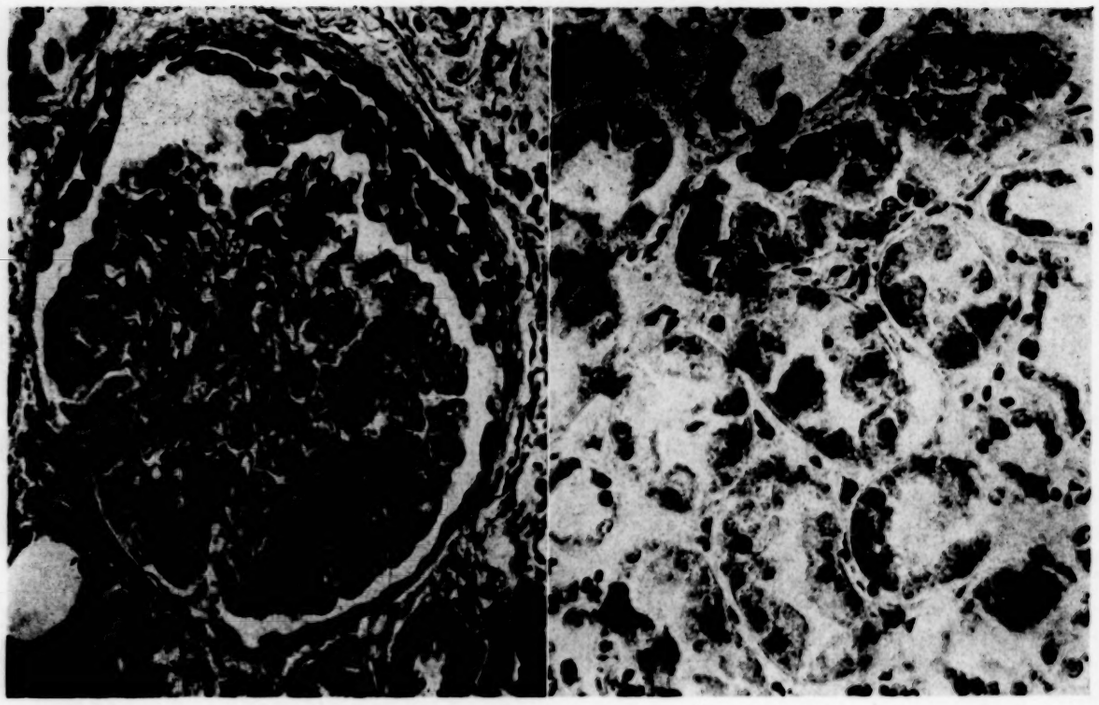
An electrocardiogram showed left axis deviation, a P-R interval of 0.20 and a QRS duration of 0.14 seconds with atypical bundle branch block. Fluoroscopy revealed a heart of normal size and clear lungs with no pleural fluid.

Digitalis glycoside was given by vein although the dyspnea was probably that of acidosis. An infusion of 5 per cent glucose in 500 cc. of saline was followed the next day by 1,500 cc. of 10 per cent glucose in distilled water. Oliguria persisted, with slight edema of the sacral region and hands. Arterial pressure was 140/85 mm. Hg. He ate poorly and complained of low backache without associated objective findings. On July 2nd the concentration of urea in the blood was 488 mg. per 100 cc. and he had four liquid, non-bloody stools. On the following morning dyspnea increased suddenly without tachycardia or other changes, and he soon became comatose, pulseless and died.

The autopsy was performed six hours after death.* There were 600 cc. of clear fluid in the left pleural cavity and 700 cc. in the right. The peritoneal and pericardial cavities did not contain abnormal amounts of fluid. The heart weighed 340 Gm. and was normal. The liver weighed 1,830 Gm. and was somewhat hyperemic. The hepatic cells toward the centers of the lobules were rather small but otherwise not remarkable. There was a small benign carcinoid tumor of the rectum and a microscopic adenoma of the adrenal cortex. The thyroid gland weighed only 8 Gm. after formalin fixation. Within it were large amounts of dense fibrous tissue infiltrated by numerous lymphocytes. This tissue separated the unusually small, empty follicles into irregular lobules. Widespread degeneration of individual fibers was seen in histologic sections of the psoas muscles and no cause could be demonstrated. There were scattered leukocytes, a few of which were eosinophiles.

The kidneys weighed 200 and 240 Gm. respectively. The surface of both was smooth and grayish-red. The cortex was 7 to 8 mm. thick and its cut surface presented some indistinct narrow red and yellowish streaks running perpendicular to the surface. A small tubular adenoma, 2 mm. in diameter, was present in one medullary pyramid on the left side. Most of the glomeruli appeared normal in histologic sections although in some there was irregular swelling and focal increase in the number of epithelial cells over the inner surface of Bowman's capsule as well as over the capillary tufts, a few of which were indistinctly separated from the capsules. Several well developed epithelial crescents were seen. (Fig. 1A.) Some glomerular capillaries were dilated and contained numerous erythrocytes, but azocarmine-aniline blue stain showed no thickening of the glomerular capillary membranes. A few glomeruli

* I am indebted to Dr. Alvin J. Cox, Jr. for the autopsy description.



A B

FIG. 1. Case I. A, glomerulus with epithelial crescent. B, small multinucleated projecting cytoplasmic masses in tubular epithelium.

completely replaced by fibrous tissue were probably unrelated to the terminal disease.

The tubules likewise showed focal changes. The epithelium of the proximal convoluted tubules was considerably swollen in many places, and the cytoplasm was more granular than usual. Only a few small colloid droplets could be seen. In a few places the swelling was more marked and nuclei were not visible or were hyperchromatic. Many of these cells had desquamated. Other convoluted tubules were smaller than normal and were frequently lined by flattened cells. A number of the tubules in the cortex had small multinucleated projecting cytoplasmic masses in the epithelial lining like those seen during epithelial regeneration. (Fig. 1B.) About 5 per cent of the sections of tubules contained hyaline or granular casts and in a few there were masses of partly disintegrated erythrocytes. Occasional tubules showed fine lipoid droplets in the cytoplasm of the lining cells but most were free from fat histologically. In scattered places within small tubules of both the cortex and the medulla there were small rounded concretions of slightly refractile transparent material which was stained by hematoxylin but did not give the reaction of calcium with the Von Kossa staining method. In several of these there were clusters of fine, needle-like structures suggesting crystals. The significance of these has not been determined.

The arteries in the kidneys were normal except for mild intimal fibrous thickening in some of the medium sized branches. The interstitial tissue of both the cortex and medulla contained a few scattered lymphoid cells and there were occasional small lymphoid nodules. The tubules of the medulla were somewhat separated from one another by more than the usual amount of fibrous interstitial tissue.

Almost all of the morphologic kidney lesions were in the tubules where there was evidence of injury to the epithelium and some regeneration. The swelling and proliferation of the glomerular epithelium was presumably related. The lesions were less striking than might be expected in view of the fatal anuria. In the autopsy protocol there is a statement that no heavy metals could be demonstrated in the kidney, but the actual records of the toxicologist could not be found.

CASE II. Mrs. D. T. (E7874), a housewife twenty-nine years of age, entered Stanford University Hospital on January 24, 1939, because of edema for one month.

There was no family history of asthma, hay fever, eczema or urticaria. However, the patient's mother, sisters and an uncle had had poison oak repeatedly on slight exposure. In

1946 the patient's daughter had poison oak at the age of five; a son aged three had escaped the dermatitis.

The patient began to have hay fever and bronchial asthma at the age of five; epinephrine had been injected frequently. She had severe dermatitis of poison oak almost annually for many years; it usually appeared in December or January, often by exposure to her husband's hunting clothes. About 1930 the ingestion of a commercial extract of poison oak was tried in an attempt at prophylaxis but was discontinued when it caused an eruption of the lips and mouth. A similar but more careful trial with a very dilute extract in 1946 appeared to be efficacious, at least it was not obviously harmful. In January, 1937, a most severe attack occurred, with "one solid blister from shoulder to wrist" on both arms; recovery required months and scars remained almost a year. Hematuria had never occurred; a routine urinalysis was negative on March 16, 1936.

The pertinent illness began with one day of headache and vomiting on December 29, 1938; swelling of the eyelids was noted within a few days and generalized edema soon appeared without other symptoms as the body weight increased between 15 and 30 pounds. There was no gross hematuria then or at any other time. The last previous attack of poison oak had started in December and was not particularly severe.

Examination showed massive pitting edema and two small healing lesions of poison oak. The optic fundi and heart were normal; arterial pressure was 115/80 mm. Hg.

Table 1 gives the results of laboratory findings and indicates the course of the illness. It may be noted that microscopic hematuria never rose above 6,000,000 erythrocytes per twenty-four hours (voided specimens) and that there was relative hemoconcentration at first. Visible lipemia was present only in serum taken March 2, 1939, when fat was present in the urine as droplets in hyaline casts and as oval fat bodies. Arterial pressure ranged irregularly from 120/85

TABLE 1

FINDINGS IN CASE II

Date	Rate of Excretion in Urine per Twenty-four Hours				Arterial Pressure (Mm. Hg)		Blood		
	Protein (Gm.)	Casts* (Thousands)	Red Blood Cells (Millions)	White and Epithelial Cells (Millions)	Systolic	Diastolic	Hematocrit (% normal)	Urea (Mg./100 cc.)	Serum Protein (Gm./100 cc.)
January 24, 1939	5.9	1200	1	25	115	80	116	15.0	5.1
January 31, 1939	11.6	500†	0.5	7	110	85	111	18.7	4.8
February 16, 1939	7.2	400	5	20	...	..	...	19.5	...
March 2, 1939	8.4	3500‡	3	16	105	80	99	16.0	5.1§
March 29, 1939	3.0	2000	5	7	120	85			
May 4, 1939	2.4	900	6	4	110	80	91	21.3	5.7
May 18, 1939	0.2	400	4	3	105	70	90	17.8	6.2
June 15, 1949	0.08	30	2	2	...	..	90	19.5	6.3
July 11, 1939	0.00	0	1	2	110	65	90	19.5	5.7
August 24, 1938	0.01	0	1	1	105	70	89	....	6.6
October 16, 1939	0.00	0	0	4	125	80	90		
November 30, 1939	0.00	0	0	3	120	80	90	19.6	
December 21, 1939	0.00	0	0	5	120	80			
February 21, 1940	0.00	0	0	2					
September 4, 1940									
October 20, 1946	0.00	....	...	..	120	80			

* All hyaline casts.
† Some with a few fat droplets.
‡ Some with many fat droplets.
§ Serum visibly lipemic.

to 105/70 mm. Hg, and the concentration of urea in the blood from 15.0 to 21.3 mg. per 100 cc. The blood Wassermann reaction was negative, the blood group A.

A diet was prescribed and potassium chloride given without benefit. Returning home after only a few days in the hospital, she was ambulatory thereafter. More than the usual amount of asthma appeared until late in March and again during August; epinephrine was used freely. The greatest part of the diuresis occurred during April.

The first of two uncomplicated pregnancies began in June, 1940. In February of 1947 she continued to be well, with normal urine; there have been only very minor attacks of poison oak. Serum taken January 31, 1947, agglutinated sheep cells in a titer of only 14.

Case III. L. C. F., a school boy twelve years of age, was seen on March 27, 1934, by Dr. Thomas Addis, who kindly supplied the following information:

There was no familial hypersensitivity but for hay fever in a cousin. The patient had laryngitis at the age of two, diphtheria at three, otitis media at four, pertussis at five, chicken pox at six and measles at nine. He had several episodes of poison oak. Urinalyses were normal.

About April 10, 1933, he was exposed to poison oak; by evening the skin of face and arms was "blotchy red." On the following morning his face was swollen and he was given an extract of poison oak orally. Within two days there were numerous bullae and generalized swelling. He improved for a few days but a week after the onset became drowsy, vomited and was anorexic. A few days later swelling of the eyelids, abdomen and ankles was noted; the urine was scanty and dark. Proteinuria was discovered April 24, 1933.

Upon admission into a hospital that day it was reported that there was slight edema of eyelids and ankles, exfoliation of the skin on the hands and an arterial pressure of 150/85 mm. Hg (128/70 three days later). There were 4,500,000 erythrocytes and 11,000 leukocytes per cu. mm. of blood; of the latter 66 per cent were polymorphonuclear neutrophiles and 6 per cent eosinophiles. The urine was clear and yellow with specific gravity 1.008; there was a moderate amount of proteinuria and the sediment contained many hyaline and a few granular casts, a few erythrocytes and leukocytes. The blood contained 29.3 mg. of nonprotein nitrogen and 237 mg. of cholesterol per 100 cc.; the concentration of protein in the serum was 4.7 Gm./100 cc. (albumin 3.3, globulin 1.4).

Findings were similar in two later hospital entries. Ascites appeared. The skin was pale but otherwise normal. Arterial pressure varied from 135/90 to 112/78 mm. Hg. Most urinalyses revealed no erythrocytes but there were casts and heavy proteinuria. Acacia given intravenously was followed by reactions with urticaria and fever; these and an intercurrent pharyngitis seemed to precede moderate diureses.

On March 27, 1934, Dr. Thomas Addis found the urine to measure 304 cc. per twenty-four hours; in this period there were 15,200,000 casts (1 per cent fatty, 1 per cent waxy, and 98 per cent hyaline with fat droplets), 600,000 erythrocytes, 24,000,000 leukocytes and renal epithelial cells, and 11.8 Gm. of protein; the specific gravity was 1.032.

Further details are lacking, but apparently the renal lesion continued with edema present most of the time until near the end. Death occurred on February 9, 1935, following uremia. Necropsy was not permitted.

Case IV. Mrs. M. G. (241047), a housewife, was twenty-nine years of age when she first entered Stanford University Hospital on April 19, 1945, because of edema for ten months.

No suggestion of the hypersensitive state was obtained in either the family or her own history.

In June, 1944, she had an intensely itching papular eruption on cheeks and a forearm which healed after four days. The dermatitis was attributed to poison oak, known to be present near her home; however, the dermatitis of poison oak had never occurred before and there had been none since. Therapy consisted only of calamine lotion. Within two to four weeks of the dermatitis the legs began to swell; there had been no sore throat or other preceding illness, and there was no gross hematuria at any time. Proteinuria was soon discovered; this and varying degrees of edema continued up to the time of her admission.

Examination in April, 1945, showed pallor, massive pitting edema and minimal ascites. Arterial pressure was 140/96 mm. Hg. The heart, optic fundi, peripheral arteries and skin were normal.

The concentration of hemoglobin in the blood was 14.0 Gm. per 100 cc. Counts showed 4,480,000 erythrocytes and 14,320 leukocytes per cu. mm.; only 2 per cent of the latter were eosinophiles. The total concentration of the

serum proteins was 4.86 Gm./100 cc., that of albumin 1.43 Gm./100 cc. The serum was inconstantly lipemic; the cholesterol content was 370 mg. per 100 cc. The concentration of urea in the blood was 36 mg./100 cc. Electrocardiograms were normal. The patient belonged to blood group O,Rh_1.

In the urine of March 20, 1945, Dr. Thomas Addis found 13.8 Gm. of protein, 2,400,000 hyaline casts, 1,500,000 erythrocytes, and 38,000,000 leukocytes and epithelial cells per twenty-four hours. There were a few oval fat bodies and fat droplets. Two years later the urine contained 10.7 Gm. of protein, 300,000 hyaline casts, 5,000,000 erythrocytes, and 15,000,000 leukocytes and epithelial cells per twenty-four hours. Many voided specimens of urine in the two years showed similar findings; the greatest number of erythrocytes per twenty-four hours was 16,000,000.

Agglutinins for sheep cells were present in a titer of 14–28 on October 15, 1946 and March 20, 1947. On January 3, 1947, Dr. Sidney Raffel found agglutinins in a titer of 128, hemolysins 64; neither antibody was absorbed by heated ox cells. The antistreptolysin titer was 50 units per cc. twice in 1947.

Despite continuing proteinuria and edema, her general status is satisfactory three years after the onset of the disease. Ambulatory most of the time, she has entered the hospital over twenty times for infusions of plasma or human serum albumin. These have been successful in inducing diuresis. Arterial pressure has varied between 130/72 and 160/110 mm. Hg but is not increasing. The most recent concentration of urea in the blood was 27 mg./100 cc.

Case v. Mr. R. J. R. (213156), a machinist of fifty-four, consulted Dr. Thomas Addis (to whom we are indebted for much of the following) on November 4, 1941, because of edema for two months.

No familial hypersensitiveness was recorded. The patient suffered typhoid fever in 1931. In 1932 he had five days of hematuria, dysuria and nocturia; these disappeared after a tooth was extracted. In 1945 there was an upper respiratory infection complicated by dental abscesses and cervical adenitis; the remaining teeth were removed.

He remained in good health until severe poison oak dermatitis occurred on September 15, 1941, with large vesicles and bullae. Three days later he became edematous and remained so after the skin healed. He felt well but for dyspnea on effort, attributed to the grossly swollen legs.

Examination showed an obese, pale man with massive generalized edema, ascites and slight hydrothorax. The optic fundi were normal and the radial arteries were thick. The heart was normal. Arterial pressure was 165/95 to 140/90 mm. Hg. The skin was normal and there was no fever.

The volume of packed erythrocytes in the blood was 93 per cent of normal. The serum protein concentration was 4.2 Gm./100 cc., the concentration of urea in the blood was 61.5 mg./100 cc. Seven urinalyses in the next two months showed: 324–512 cc. per twenty-four hours, with specific gravities of 1.035 to 1.024. The rates of proteinuria were 6.6–16.3 Gm. per twenty-four hours, and in that interval the sediment contained 6–40 million erythrocytes, 18–81 million leukocytes and renal tubular cells including oval fat bodies and 6.4–48.6 million casts (chiefly hyaline with fat droplets, none of red blood cells).

Angina pectoris appeared later in November. An electrocardiogram showed left axis deviation, low voltage of the QRS complex and T waves, and a Q wave in lead III. A roentgenogram revealed small amounts of pleural fluid bilaterally and a heart normal in size. A gallop sound was heard inconstantly. Digitalis was added to treatment with nitroglycerine, vitamins and diet. Abdominal paracentesis yielded some 4 L. of pseudochylous fluid.

He entered Lane Hospital in May, 1942. Anasarca was still present. There were no additional physical findings. Arterial pressure was 140/90 mm. Hg. The concentration of hemoglobin was 13.8 Gm./100 cc., and there were 4,380,000 erythrocytes and 6,900 leukocytes (normal differential count, 1 per cent eosinophiles) per cu. mm. Urinary findings were unchanged. The lipemic serum contained 397 mg. of cholesterol and 3.0 Gm. of protein per 100 cc. The Wassermann reaction was negative. The electrocardiogram showed no change. Three infusions of plasma (250 cc.) were followed by a loss of only 5.5 Kg. in two weeks; the third produced orthopnea.

Without much change he returned to the hospital in July, 1942. The concentration of urea in the blood was 66 mg./100 cc., that of protein in the serum 4.0 Gm./100 cc. Urinary findings were similar to those given above. An infusion of plasma was scarcely completed when he suffered severe and continuing substernal

pain; the electrocardiogram showed changes compatible with myocardial infarction. He died within an hour; permission for necropsy could not be obtained.

CASE VI. Miss M. H. (E55127), a clerical worker nineteen years of age, entered Stanford University Hospital October 18, 1946, because of "kidney trouble."

The father had hay fever so badly that he had to move his family, unfortunately to an area in which poison oak abounds. There were no other members with hypersensitive states.

In childhood the patient had measles, mumps and impetigo; the last occurred again in January, 1946. She often had to leave school because of severe urticaria, perhaps related to strawberries and tomatoes. Hay fever occurred once but not eczema nor asthma.

Extensive dermatitis of poison oak appeared almost annually between 1938 and 1944, occasionally enforcing rest in bed for periods up to five weeks at a time. A commercial preparation of poison oak was taken by mouth fairly steadily since 1944 and may have prevented dermatitis at least for a time.

In January, 1945, the ankles and calves became swollen, the last previous bout of poison oak having ended in October, 1944. In February the eyelids also swelled; a blood count was said to have been normal then and the urine not unusual in appearance, but it was not analyzed and the arterial pressure not determined. After another month the edema disappeared, only to return eight to ten times since at intervals of a few months and for a few weeks at a time. The urine was never bloody and was examined several times with negative results while edema was present.

In late July, 1946, poison oak again caused dermatitis but this was not severe. While it was healing, with only a few lesions on the arms, swelling of the eyelids and ankles appeared on August 24th and there were headaches. Edema lasted only a week. No urinary abnormalities were noted but there was no analysis. Symptoms interpreted as "flu" very late in August were followed by a slightly productive cough. By September 10th there was a low grade fever. Hospitalized elsewhere September 23 to 25th, her temperature was reported as 39°c. and her throat reddened but nothing was said of cough and urine. Penicillin was given with subsequent relief of chills and fever. Frontal headaches continued and right lumbar backache commenced at about this time.

On October 6th edema returned and was severe two days later when the urine became brown without oliguria and was found to contain protein, erythrocytes and leukocytes; it was further reported that the arterial pressure was 136–140/90 mm. Hg. One wrist ached temporarily but without swelling on October 12th.

Her general appearance was good; she was ambulatory and there was no fever. The eyelids were not swollen and the optic fundi were normal. The tonsils were small and fibrotic. There was no lymphadenopathy. The lungs were clear and the heart and abdomen perfectly normal. The right lumbar region was tender. There was very slight pitting edema of the ankles, none at the sacral region. Arterial pressure was 125/80 mm. Hg. The joints and skin were normal.

The concentration of hemoglobin was 15.7 Gm./100 cc., and the blood contained 5,200,000 erythrocytes and 14,000 leukocytes per cu. mm. Of these, 78 per cent were polymorphonuclear neutrophiles, 11 per cent lymphocytes, 4 per cent monocytes and 7 per cent eosinophiles (980 per cu. mm.). The sedimentation rate was 23 mm. per hour (Cutler). The blood contained 33 mg./100 cc. of urea, serum cholesterol was 830 mg./100 cc. without visible lipemia, and the serum protein concentrations were globulin 1.4, albumin 2.6 and total 4.0 Gm./100 cc. An electrocardiogram was normal as was a roentgenogram of the chest.

The urine had a pH of 7.0 with specific gravity of 1.015. It measured 1,088 cc. per twenty-four hours, in which period there were excreted 8.8 Gm. of protein, 100,000 casts (hyaline with heavy fatty inclusions; in several examinations, only one cast thought to be a red blood cell cast was seen), 450,000,000 erythrocytes, 150,000,000 leukocytes and renal tubular epithelial cells exclusive of 12,000,000 oval fat bodies.

Heterophile antibodies, entirely (98 per cent) absorbed by guinea pig kidney but not at all by heated ox erythrocytes (Dr. Sidney Raffel) agglutinated sheep cells in serum dilutions up to 128, while hemolysis of sheep cells took place in dilutions of 128 to 1024. Antistreptolysin titer was 12 units per cc., the cold agglutinin titer 1:4. There were no agglutinins against E. typhosus H and O, S. paratyphosa A, S. Schottmülleri, Br. abortus, or Pr. OX2, HX2 and OXK. Agglutination against Pr. OX19 was negative in the tube, positive 1:40 on the slide. The blood Wassermann reaction was

negative. The patient belonged to blood group O,Rh_1.

Management consisted of a diet containing a minimum amount of salt, 40 Gm. of protein and sufficient calories to maintain body weight. She was dismissed from the hospital October 25th. By December 14, 1946, the edema had gone and the back seldom ached. In the next three months there were many febrile episodes, including those associated with acute frontal sinusitis and lobar pneumonia. It was not possible to make bacteriologic examinations but the antistreptolysin titer did not rise. Neither gross edema nor hematuria recurred but the intensity of the renal lesion increased. Further findings are given in Table II. Proteinuria has now persisted for fifteen months; the arterial pressure has averaged 130/85 mm. Hg.

TABLE II
FINDINGS IN CASE VI

Date	Rate of Excretion in Urine per Twenty-four Hours					Serum						
	Protein (Gm.)	Casts (Thousands)	Red Blood Cells (Millions)	White and Epithelial Cells (Millions)	Oval Fat Bodies (Millions)	Lipemia	Cholesterol (Mg./100 cc.)	Proteins (Gm./100 cc.)		Titer		
								Total	Albumin	Antistreptolysin (Units/cc.)	Heterophile	
											Agglutinins	Hemolysins
October, 18, 1946	8.8	100	450	150	12	0	830	3.98	2.56	12		
October 21, 1946	8.4	60	300	120	20	..	...	....	....	..	128	512
November, 16, 1946	7.2	400	45	120	+	++	630	4.65	3.23			
December, 14, 1946	7.2	100	100	30	0	++	...	4.55	2.73	12	64	128
February 8, 1947	5.6	100	150	50	+							
March 29, 1947	4.8	0	450	225	8	+	455	4.80	...	12	128	1024
May 29, 1947	4.0	0	150	220	0	±	430	5.35	3.10	12	40	160
September, 2, 1947	4.2	0	225	15	0	..	400	5.45	3.80	12	128	256

CASE VII. A. H. (261081), a schoolboy thirteen years of age, entered Lane Hospital February 25, 1947, because of "blood in the urine" for six weeks.

His father had hay fever and a sister had urticaria. The patient had had severe hay fever. He suffered the dermatitis of poison oak four or five times, the last episode two years previously. His general health had been good.

The dermatitis of poison oak appeared on November 30, 1946. The lesions were confined to the ankles and were thought to have been infected secondarily after scratching. They seemed to be clearing, but about December 18th the ankles became covered with moist, dark lesions. Lymphangitis and inguinal lymphadenitis were found and raised erythematous lesions appeared on the forearms. He entered another hospital on December 22nd. There was a low fever (to 38°c.). The urine was normal. Penicillin was started that day. Two days later he had an urticaria-like eruption with vomiting and abdominal discomfort. The lesions promptly disappeared and the infection was pronounced healed.

On December 29, 1946, two days after stopping penicillin and dismissal from the hospital, coffee-colored urine appeared and red blood cells were found in the sediment. The eyelids were puffy. Both flanks ached for a few days. The throat was not sore at any recent time. The urinary abnormalities persisted and he was

referred to Dr. Thomas Addis who advised hospitalization.

Upon examination he appeared well. There was no fever. Arterial pressure ranged from 125/80 to 115/75 mm. Hg. The optic fundi were normal. The tonsils were large and contained pus in the crypts, and there were a few very small, non-tender cervical lymph nodes. The heart was not remarkable but for a moderate systolic blowing murmur at the apex. There was no edema. There were many healed areas of discoloration over both ankles and legs.

The concentration of hemoglobin was 12.5 Gm./100 cc., and the blood contained 4,950,000 erythrocytes and 7,000 leukocytes per cu. mm. Of these there were 63 per cent polymorphonuclear neutrophiles, 24 per cent lymphocytes, 12 per cent monocytes and 1 per cent eosinophiles. The corrected sedimentation rate was 8 mm. per hour. The concentration of protein in the serum was 5.0 Gm./100 cc. of which 3.2 was albumin and 1.8 globulin. The concentration of cholesterol in the serum was 239 mg./100 cc; that of urea in the blood was 32.0 mg. and that of creatinine in the serum was 1.37 mg./100 cc. Of phenolsulphonphthalein injected intravenously, 65 per cent was excreted in two hours. An electrocardiogram and roentgenogram of the chest were normal. The circulation time (decholin) was 14 seconds, venous pressure 10.5 cm. Culture of the tonsils revealed a heavy growth of group A hemolytic streptococci; the antistreptolysin titer was 166 units per cc. on both February 25th and March 29th but fell to 100 units per cc. on April 26, 1947. The serum agglutinated sheep cells in a dilution of 1 :14.

On February 20th the urine contained 5.7 Gm. of protein and 3,840 million erythrocytes per twenty-four hours, rare granular casts (red blood cell casts were found later) and 240 million white blood and renal epithelial cells. On April 26th after five weeks of rest in bed and a diet low in protein, the urine for twenty-four hours contained only 0.06 Gm. of protein, 210,000,000 erythrocytes and 30,000,000 white blood and renal epithelial cells. Oval fat bodies were not observed.

COMMENTS

Diagnoses. Case I was regarded primarily as one of tubular degeneration with necrosis and anuria, not unlike the "lower nephron nephrosis" syndrome.[2] In Cases II to V the nephrotic syndrome was prominent. Cases II, III and IV were thought to be examples of pure lipoid nephrosis; chronic glomerular nephritis was considered present in Case V. Cases VI and VII seemed to be instances of the initial stage of glomerular nephritis; there was a prominent component of tubular degeneration in Case VI as well as a suggestion of periarteritis nodosa (myalgia and arthralgia). In six of the seven cases tubular degeneration or the nephrotic syndrome were present.

It may be noted that the renal complications became obvious in from three days to two months after the onset of dermatitis, usually in one to four weeks. In three patients manifestations of renal disease occurred coincident with the period of recovery from dermatitis.

Other Cases. In addition to these patients, we have heard undocumented reports of four instances of "nephrosis" with one death in some 3,000 to 4,000 soldiers hospitalized for poison oak dermatitis; further details were not available. A syndrome not unlike that of Case I occurred in a man while severe dermatitis of poison ivy was healing;[3] it was attributed to injections of a mercurial diuretic given for congestive heart failure and to acute glomerular nephritis. According to the protocol, oliguria and edema appeared before the first injection of the mercurial and about a week after the more or less simultaneous subsidence of the dermatitis and stopping of digitalis; hematuria was microscopic only. An instance of what appeared to be ordinary glomerular nephritis[4] followed infected dermatitis venenata (sumac?). Finally, a case regarded as one of periarteritis nodosa subsequent to poison oak has been described.[1]

Coincidence and Infection. In the patients just described, renal complications, especially with tubular degeneration, appeared in close temporal relationship to the healing of poison oak dermatitis. It is recognized that this by no means establishes an etiologic relationship; in Cases IV and V particularly there are no clear past histories of dermatitis and one may be dealing only with coincidence. It is even possible that the occurrences in all of these patients are merely a series of coincidences; satisfactory

data are not available on the incidence of poison oak dermatitis and renal lesions and the problem has not been approached by statistical methods.

Dermatitis of any sort may lead to secondary infection; perhaps it is this factor which is responsible for the subsequent renal involvement. In Case VI there was a suggestion of infection not of the skin but of the respiratory tract; repeated determinations over a period of eleven months showed the antistreptolysin titer to remain at 12 units per cc., but similar low levels have been found even after streptococcal infections in some patients with the nephrotic syndrome.[5,6,7] In Case VII the skin was infected with an unknown organism, and many hemolytic streptococci of group A were recovered from the tonsils in the absence of sore throat. The antistreptolysin titer was 166 units per cc. on each of two occasions one month apart (similar or higher levels occur in 24 per cent of individuals before and in 77 per cent after a hemolytic streptococcus infection[8]); the fall in titer to 100 units per cc. after one more month is in favor of a streptococcal infection.

It is certainly noteworthy and perhaps significant that in this series of patients gross hematuria and red blood cell casts were found only in the two cases with suspected or definite infection. As noted, a patient similar to the one in Case VII has been reported[4] as an instance of glomerular nephritis following dermatitis venenata (sumac?) with secondary, unidentified infection of the skin and streptococci in the throat; the antistreptolysin titer was not determined. It seems quite likely that under these conditions the dermatitis of poison oak or related species is not primarily responsible for the ensuing nephritis; it then merely serves as a portal of entry for the hemolytic streptococcus.

TOXIC PRINCIPLE OF POISON OAK AND RELATED PLANTS

Others have well reviewed the chemical and immunologic evidence for the identity of the toxic substance found in poison oak, poison ivy and sumac in this country, in the Japanese lac tree and perhaps in the mango.[9–13] This agent appears to be urushiol, also known as lobinol and toxicodendrol, a catechol compound (other similar compounds may be present) with an average of two double bonds in a hydrocarbon side chain. The molecule has the properties of general toxicity and ability to induce sensitization, at least of the skin.

Direct Toxic and Nephrotoxic Effects. Older literature contains a few references, poorly documented, to severe systemic reactions and death after exposure to rhus. These occurred as results of eating the fruit,[14] chewing the leaves,[15] drinking decoctions[16,17] or of dermatitis upon contact.[18,19,20] The prophylactic or therapeutic employment of modern preparations has also been followed by severe reactions.[21,22] Although local and generalized edema is frequently mentioned by the authors just cited, the urine was generally normal upon the few occasions when it was examined. McNair, however, found proteinuria in one-third of his patients hospitalized with severe dermatitis.[23,24] His one case of "acute nephritis" is not convincing and there was no mention of any continuing renal lesion; the findings probably represented the proteinuria common in acute illness, particularly in the presence of fever. More recently, proteinuria was not found in a group[25] similar to that studied by McNair.

Only four reports have been found pertaining to renal changes after administration of the toxic principle to animals. The most specific claimed that "the irritant properties of toxicodendrol were most marked on the kidneys, producing nephritis and conspicuous fatty degeneration of this organ";[26] anuria occurred, followed by the appearance of protein, blood cells and renal epithelium in the urine. Poorly described renal changes were found by two other observers[27,28] but not by another.[29]

Although the foregoing observations suggest that there is literally more to poison oak dermatitis than meets the eye, they are completely inadequate as an explanation of events in these patients. If renal involvement had been the immediate result of any

directly acting nephrotoxin, one might have expected its appearance at the height of the dermatitis rather than at or after the stage of recovery; moreover, chronic renal lesions would not be likely.

Hypersensitive State and Poison Oak. Such considerations lead to the proposition that the renal lesions following poison oak in these patients may have been the result of sensitization. All but two patients were known to have suffered repeatedly from the dermatitis, often acquired on slight exposure to the plant. Four had sought relief in the use of commercial extracts of poison oak; in two of the three fatal cases (Cases I and III), in a severe case of periarteritis nodosa[1] and possibly in a fatal case after poison ivy[3] extracts were unfortunately used in therapeutic attempts.

Upon their first exposure to the plant or its extract neither infants nor adults react with dermatitis.[9] Some individuals are highly resistant to heavy exposure[30] in spite of evidence that strong concentrations have a direct vesicant activity unrelated to sensitization.[31] Most workers, however, agree that poison oak (ivy, sumac) dermatitis is a sensitization phenomenon.[9] The associated chemical and experimental problems continue to receive attention[9–13,32,33,34] more than a decade after the demonstration that guinea pigs could be sensitized to poison ivy.[35,36]

Some immunologic aspects of the sensitization induced by exposure to poison oak have recently been reviewed;[9] it appears to be similar to cutaneous sensitization induced by other plants and their extracts or by certain chemicals and metals, but it is thought to differ from that responsible for hay fever or bronchial asthma. Antibodies have not been demonstrated either *in vitro* or by passive transfer. It is not altogether clear whether the gastrointestinal involvement after ingestion of the leaves or their extract[10] represents a direct vesicant activity or sensitization; with this possible exception and ignoring a cough sometimes noted during the dermatitis, the skin seems to be the only tissue in which sensitization has been reported[23,24] but this point has not been studied extensively or recently. Attention should be directed to a single case in which a reaction resembling encephalitis followed ingestion of a tincture of poison ivy,[22] a reaction which assumes further interest in the light of modern studies on sensitization in the central nervous system.[37]

It has recently been shown that the intraperitoneal injection of simple chemical compounds which are skin sensitizers results in the formation of precipitins detectable *in vitro* with a gelatin conjugate of the sensitizer.[38] The authors did not work with urushiol but indicated that such a pro-antigenic substance might be metabolized to a derivative (quinone) capable of conjugation with protein and the production of incomplete antibodies. In this connection it may be noted that sensitization of the skin has been produced by intraperitoneal injections of extracts of poison ivy.[11]

Renal lesions and antibodies to kidney have been demonstrated in animals injected with homologous renal tissue to which bacterial toxins had been added.[39,40] This suggests, as pure speculation, that the products of poison oak may also incite antigenicity of renal tissue with consequent formation of autoantibodies.

Heterophile Antibodies. Heterophile antibodies do not appear to have been studied in relation to rhus dermatitis. The Forssman substance so widely distributed in nature[41,42,43] could not be demonstrated by Dr. Sidney Raffel[44] in a commercial extract of poison oak. The titer of sheep cell antibodies was determined in the sera of four patients in this series. In Case II the titer was only 14 seven years after healing of the renal lesion and eight years after its onset. The same low titer was found in Case VII, with initial glomerular nephritis which was probably the result of streptococcal infection. In Case IV (pure lipoid nephrosis or the nephrotic syndrome with chronic glomerular nephritis) Dr. Sidney Raffel[44] found sheep cell agglutinins in a titer of 128, hemolysins 64. In Case VI (initial stage of glomerular nephritis with nephrotic

component) he found the titer of agglutinins 64–128, that of hemolysins 128–1024. In Case VI the antibodies were 98 per cent absorbed by guinea pig kidney while they were not absorbed by heated ox erythrocytes in Cases IV, VI, or VII.

Parenthetically, it may be noted here that the titer of sheep cell agglutinins was only 7 in a patient with periarteritis nodosa which followed poison oak,[1] but the determination was not made until seven years after the onset. The titer was only 28 in a patient in whom moderately severe but uncomplicated dermatitis had been caused by an injection of rhus extract. On the other hand, moderate elevations of Forssman type antibodies have been found in the sera of other patients with the nephrotic syndrome.

The significance of the findings is not as yet clear. At the moment the presence of heterophile antibodies in these patients does not appear to be related directly to poison oak or sensitization phenomena[41] but rather to alterations in the serum proteins accompanying the nephrotic syndrome.

Hypersensitive State and the Nephrotic Syndrome. As pointed out earlier, renal tubular degeneration or the nephrotic syndrome were prominent in six of the seven patients (Cases I to VI). The hematuric features of glomerular nephritis were outstanding only in those two patients (Cases VI and VII) in whom complicating infection appeared probable, and in another patient[1] thought to have periarteritis nodosa. Recent publications concerned with the rôle of hypersensitivity in the experimental production of arterial and glomerular lesions[39,40,45,46] have supported older views on the pathogenesis of periarteritis nodosa and glomerular nephritis.

Many authors have commented on the similarities between serum sickness and certain features of the initial stage of glomerular nephritis. However, relationships between the hypersensitive state and the nephrotic syndrome in general or pure lipoid nephrosis in particular do not appear to have been stressed. This type of syndrome is generally attributed more or less vaguely to infection; in fact, it is not altogether clear whether pure lipoid nephrosis is primarily a metabolic or a renal disorder. Consideration of information available in the literature and of clinical observations suggests strongly that hypersensitivity may sometimes play a prominent part in the pathogenesis of the nephrotic syndrome; the evidence bearing on this point cannot well be given here.

SUMMARY AND CONCLUSIONS

In seven patients renal disturbances appeared during or shortly after the stage of recovery from the dermatitis of poison oak.

In one patient the typical initial stage of glomerular nephritis was probably the result of streptococcal infection. Of all the cases this one was least likely related causally to poison oak.

In another there was fatal anuria with tubular degeneration. A somewhat similar case following poison ivy has been reported by others.

In the remaining five cases renal tubular degeneration was also prominent. The nephrotic syndrome appeared in at least four; three of which were thought to be instances of pure lipoid nephrosis.

The available information relative to the toxic and sensitizing activities of poison oak and related plants was reviewed. The possibilities of explaining the findings by coincidence or infection were considered.

It seems possible and even probable that the renal abnormalities in most of these patients were the result of sensitization induced by poison oak. Final proof, of course, is lacking.

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Primary Carcinoma of the Liver*

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SINCE the time of Virchow, primary carcinoma of the liver has been considered rare. During the past eighteen months we have observed five cases in approximately 500 consecutive cases autopsied at the School of Medicine of the University of Alabama. The difficulty in arriving at a reliable diagnosis of this disease has prompted us to discuss only those cases proved at autopsy. The incidence of 1 per cent in our small series is one of the highest recorded occurring in inhabitants of the western world. Counsellor and McIndoe[1] give the incidence of primary carcinoma of the liver in 42,276 autopsies as 0.14 per cent. Fox and Bartels[2] found this disease in 0.133 per cent of the subjects in 29,215 necropsies. White[3] records an incidence of 0.13 per cent in 18,500 autopsies at Guy's Hospital, London. Goldzieher and Bokay[4] and Fried[5] report a somewhat higher incidence, 0.3 per cent, the first in a study of 6,000 and the latter in 1,200 autopsies. Strong and Pitts[6] report a total incidence of 0.61 per cent in 1,967 autopsies in Vancouver, British Columbia. In the latter report, however, there were ten cases of the disease in 139 Chinese patients who came to autopsy, an incidence of 7.19 per cent. Rosenthal[7] records that in 2,091 autopsies at Cook County Hospital, Chicago, during 1929 to 1935, there were twelve cases of primary carcinoma of the liver, or 0.57 per cent. Rowan and Mallory[8] report nine in 6,500 autopsies, or 0.13 per cent; Clawson and Cabot[9] five in 5,100 autopsies, or 0.09 per cent and Torland[10] ten in 6,000 autopsies, or 0.16 per cent. The literature shows the tumor in an average of 0.5 per cent of cases coming to autopsy.

The incidence of primary carcinoma of the liver has a definite geographic distribution. It is seen more commonly in Asiatic and South African countries. Nagayo[11] reports that in Japan primary carcinoma of the liver ranks from third (in males) to sixth (in females) in occurrence of malignant diseases in that country. In China and Korea it also ranks high. Tull[12] reported finding sixteen cases of primary carcinoma of the liver in 1,312 autopsies in Singapore. The prevalence of the disease among Filipinos is demonstrated by the incidence of the disease at the Manila General Hospital as cited by Reed and DeLeon;[13] of 1,502 cases to malignancies occurring in that hospital, 1910 to 1914 and 1922 to 1926, 950 or 6.32 per cent were primary carcinoma of the liver.

The Orientals, especially the Chinese, have been shown to have a particularly high incidence of this disease. The prevalence of animal parasite infestation, especially flukes, with resultant cirrhotic changes in the liver has been proposed as the reason for the high incidence of hepatic cancer among Orientals.

Investigators have been instituting a survey in an attempt to explain why primary liver cancer is one of the leading causes of mortality from malignant diseases in Japan in contrast to findings in other countries. Sasaki and Yeshida[14] were able to induce primary cancer of the liver in mice and rats by adding certain azo dyes, especially butter-yellow, to the diet. The occurrence of this azo dye as a coloring agent in the Japanese diet may possibly be a factor which has contributed to the high incidence of this disease in Japan. Orr[15] working in this country has confirmed these observations. He expressed the opinion that the primary effect of butter-yellow on the

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liver parenchyma is destructive and that the resultant proliferative changes are in the nature of regeneration.

Prates[16] reported a series of eighty-five cases among members of the Bantu race in South Africa. Here also the incidence of parasites in the subjects was extremely high, but the author believed that it was not a significant etiologic factor inasmuch as parasitism exists in most natives throughout the tropics without necessarily being associated with primary carcinoma of the liver. In this race the disease occurs especially among young and healthy individuals and the possibility of a dietary factor as an etiologic agent has been proposed to explain the high incidence of the disease.

INCIDENCE

Age. Primary carcinoma of the liver does not exempt any age although it is rarely found in very young children. One case in the series reported here was of a young male fourteen years of age. Steiner[17] reported a case in a male of four months. The fact that primary carcinoma of the liver is found in the very young has evoked the supposition that perhaps these tumors arise from embryonic rests.

Steiner,[17] in his review of the literature, reported seventy-five proved cases in children up to sixteen years of age. In that series 53.2 per cent of the carcinomas occurred in infants under the age of two years, 68 per cent of whom were males. A high percentage of cases occur between fifty and sixty years of age. Three of the cases reported in this paper were in this latter age group.

Sex. It is the universal opinion that primary carcinoma is more prevalent in males than females. For each female there are six males reported with this condition. Many theories have been advanced in an effort to explain this variation. It may be due to the fact that liver cell carcinomas are more frequently preceded by cirrhosis, which is more common in males whereas bile duct carcinoma, preceded by bile duct infections, is found most often in women.

The fact that cirrhosis of the liver plays an important part and is a predisposing factor in the formation of primary carcinoma of the liver is agreed on by practically all authors on the subject. Cirrhosis was present in three of our five cases. Blumenau[18] studied the autopsy findings in 198 cases with a diagnosis of cirrhosis. He found that 3.5 per cent of those in the series had primary carcinoma of the liver. Rosenthal[7] found that primary hepatic malignancies occur more frequently in cirrhosis with hemochromatosis than in cirrhosis alone. Yamagiva[19] found cirrhosis in 85 to 100 per cent of hepatomas and in 50 per cent of cholangiomas. Fried[5] postulates the theory that cirrhosis is a reparatory process arising in response to injury. This process is characterized by hypertrophy and hyperplasia of liver cells, resulting in the formation of multiple adenomatous nodules which are potentially malignant. To further elaborate on this important process Glynn[20] described a case in which hyperplasia, adenoma and cancer were all found in the same specimen. The vicarious proliferative process for some unknown reason oversteps the normal and takes on the autonomous character of the new growth. Lynch[21] in attempting to explain the apparent increase of the disease in recent years suggested that it might be related to a more frequent occurrence of a predisposing disease of the liver of the sort which appears to excite proliferation of liver cells, both parenchymal and duct, in notable degrees. In acute yellow atrophy, following recovery, there is more growth of liver and bile duct epithelium than in true portal cirrhosis. It is on the basis of this difference that healed acute yellow atrophy may predispose more to the production of carcinoma.

CLINICAL MANIFESTATIONS

The clinical features, symptoms and diagnosis of primary carcinoma of the liver vary considerably. A review of the literature shows definitely that there is no uniform clinical course which characterizes this disease. In fact, the diagnosis in the vast

majority of the cases reported in the literature was made at autopsy.

The most commonly observed symptoms and signs in our series of patients were palpable abdominal mass, weight loss, right upper quadrant pain, jaundice and ascites.

Abdominal Mass. A distinct mass was palpated in three of the cases reported herein. In all instances the mass was in the right upper quadrant of the abdomen and easily recognized by its protruding above the surrounding level of the abdominal wall. It was always firm, often irregular and only slightly if at all tender. Splenic enlargement was a fairly constant feature. This latter finding was probably due to the underlying cirrhotic process in which splenomegaly is a common finding. Approximately three-fourths of all the cases reviewed had a definitely perceptible abdominal mass.

Pain. This symptom in primary carcinoma of the liver is rarely severe early in the disease but occurs in the majority of cases as was true in our experience. The location of the pain is usually in the epigastrium or under the right costal margin. It is frequently referred to the back and is generally described as a dull, heavy ache and fairly constant in occurrence. The pain is probably due to the expansile mass with resultant distention of the capsule of the liver. The pain encountered could arise from a number of other conditions and is not characteristic; it is therefore of little value in diagnosis. Wilbur[22] reported that 72.5 per cent of his patients had upper abdominal pain.

Gastrointestinal Complaints. This complaint was not a common symptom in the cases reviewed; when present it was usually nondescript in character. No definite symptom complex of this nature has been described in the literature.

Jaundice. Four of our five patients were jaundiced either at the time of admission or subsequently in the course of the disease. The degree of jaundice present was variable, with icteric index values of 16 to 33 units. As a rule, jaundice in this disease is not intense but a fairly constant feature. Ewing[23] found that over one-half of the patients he described had chronic jaundice. Greene[24] suggests that the cause of the jaundice may be an obstruction to the outflow of bile caused by the intrahepatic tumors or possibly by enlargement of the hilar lymph glands due to metastasis of the tumor growth. Abel[25] believes the jaundice to be due to cachexia with resultant entrance into the circulation of toxic products from the malignant growth.

Ascites. Ascites was present on admission or developed after admission in three of our patients. The fluid was generally blood-tinged. Pathologic examination of the fluid for malignant cells was unsatisfactory. Sixty-six per cent of the cases described by Ewing[23] had ascites. Other authors found a comparable number. The amount varied from slight amounts not easily detected to large amounts causing marked distention of the abdomen. The presence of ascites may be explained on the basis of a cirrhotic liver inasmuch as the latter condition usually precedes primary carcinoma of the liver.

Weight Loss. In reviewing the literature weight loss was a fairly constant feature, as with our cases. Although the loss of weight was not as evident as is seen in a majority of malignant diseases, it occurred in approximately one-half of the cases reviewed. Four of our five patients complained of weight loss prior to admission to the hospital.

Peripheral Edema. Peripheral edema was not a prominent feature in our cases. Plasma protein determinations were not made in enough cases to evaluate the importance of a low albumin level as an etiologic factor in the production of edema. The same factors that produce ascites cause peripheral edema of lower extremities; Therefore, it could be expected in a like number of cases. Such is true in case reports of some workers who found that 42.5 per cent had this complication.[26]

Bleeding. In one of the cases presented massive hemorrhage was the presenting symptom and caused the rapid demise of

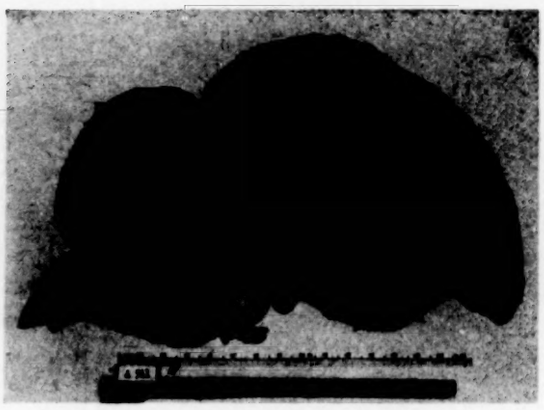

FIG. 1. Primary carcinoma of the liver, liver cell type. Note the many intrahepatic metastases.

the patient. At autopsy this fatal hemorrhage was found to be due to rupture of an esophageal varix. In reviewing the literature hemorrhage was a prominent feature of this disease. Wilbur[22] reported recurring epistaxis in four cases, hematemesis and melena in three. Fatal bleeding from esophageal varices occurred twice in this series and fatal epistaxis once. Matthews[27] thought that fatal bleeding from varices and from tumors perforating the capsule of the liver was common. In only one of our cases was the prothrombin content of the plasma estimated. A deficiency of this factor occurring from the inability of the liver to utilize vitamin K may play an important part in the production of bleeding tendency in this condition.

Diet. In no case could diet be blamed as an important factor in the production of the disease. Wilbur[22] found 22.5 per cent of his patients had used alcohol in considerable quantity but from his data he could not form any opinion as to the importance of this factor in the production of primary carcinoma of the liver.

Blood Picture. There was moderate anemia and the leukocyte count was elevated in more than one-half of the cases. Eosinophilia was present in one subject. The significance of the latter finding is not apparent but it is probably a manifestation of the malignant disease itself. No typical blood picture has been described by authors on this subject; a varied pattern such as we found was seen in most cases.

Roentgenologic Findings. As would be expected this diagnostic method was of little aid. This is to be expected in view of the difficulty of visualizing changes other than those in the size of the liver. Plates showing elevation of the right dome of the diaphragm would be suggestive of this disease process.

Stools. This laboratory procedure failed to reveal any evidence of parasitism in two patients. This finding should be of negative value in diagnosis inasmuch as parasitic infection of the liver could present a very similar picture.

Liver Function Tests. The liver function tests as a rule were disappointing as a method of diagnosis of primary carcinoma of the liver. Damage must be extensive before any appreciable change can be detected in the function tests.

In every case the course of the disease was short. Once symptoms developed to the point that an abdominal mass is palpable and there is jaundice and ascites the course is generally rapidly downhill. Moderate elevation of temperature was seen in most of our patients in the terminal stage. Boyd[28] states that fever is present in 10 per cent of the cases and attributes this to marked necrosis found in cases with massive involvement of the liver.

PATHOLOGIC FINDINGS

Primary carcinoma of the liver is classified according to the most likely origin of the malignant cells. The liver cell type of primary carcinoma of the liver is composed of chords, strands and sheets of large, polygonal cells with pinkish cytoplasm and large vesicular nuclei. (Fig. 2.) These cells resemble liver cells and are capable of producing bile both in the primary tumor and in the tumor metastases. This type is the most common primary carcinoma of the liver. Wilbur[22] reported an incidence of approximately 92 per cent liver cell carcinomas in his review of forty-nine adult cases. Steiner[17] reported fifty-two liver cell carcinomas, three bile duct carcinomas and twenty-two undifferentiated carcinomas in his report of seventy-seven primary car-

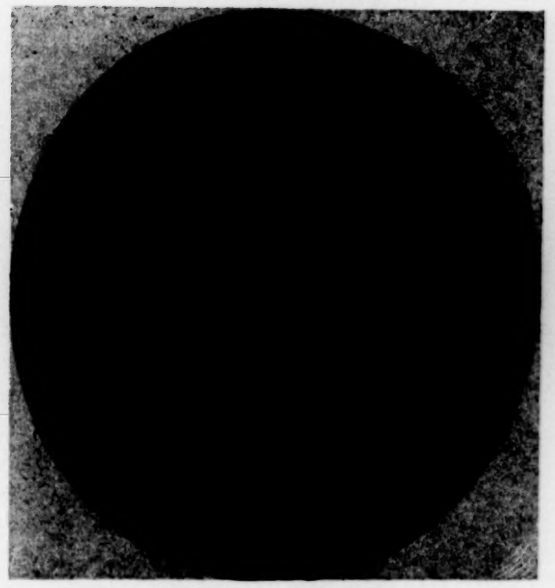

FIG. 2. Liver cell carcinoma. The liver tissue is seen here surrounded by carcinoma; no cirrhosis is present.

FIG. 3. Primary carcinoma of the liver, bile duct type.

cinomas of the liver in children under the age of sixteen. The bile duct carcinoma arises from the intrahepatic bile ducts. It assumes the appearance of an adenocarcinoma and has a tendency to form tubules and atypical alveolar apices. (Fig. 4.) In this type of carcinoma there is no secretion of bile. The cytoplasm of the cells is lighter staining and more basophilic. The nuclei are hyperchromatic. The stroma in the bile duct carcinoma is made up of connective tissue and tiny capillaries.

Primary carcinomas of the liver not infrequently show both liver cell carcinoma and bile duct carcinoma in the same tumor. This may be classified in a third group, mixed carcinoma. This, however, is the rarest type.

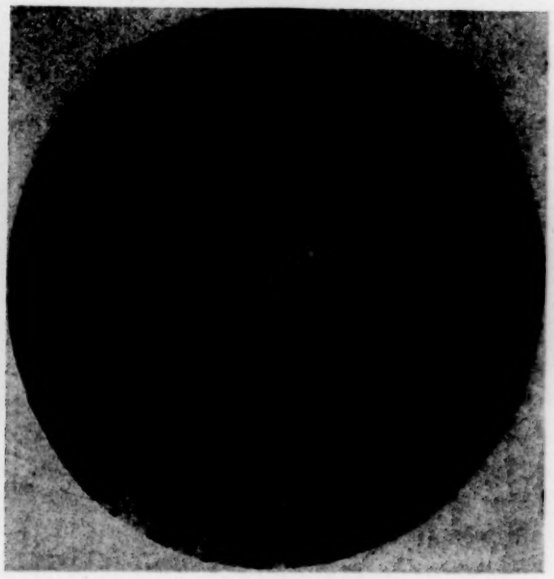

FIG. 4. Bile duct type primary carcinoma of the liver. Note the atypical bile duct formation. Cirrhotic liver is seen above and below the carcinoma.

Three of the carcinomas reported here were of the liver cell type. (Fig. 1.) The other two were bile duct carcinomas. (Fig. 3.)

Although there is some disagreement regarding the development of primary carcinoma of the liver, the generally accepted theory is that they have a unicentric origin. This theory maintains that the multiple nodules of tumor tissue within the liver represent intrahepatic metastasis. A much smaller group believe primary carcinomas of the liver have a multicentric origin.

Intrahepatic metastases are very frequent in primary carcinoma of the liver. This is particularly true in the liver cell type. Extrahepatic metastases are infrequent. Steiner[17] in his review of primary carcinoma of the liver in children found that extrahepatic metastasis occurred in 27.2 per cent of the seventy-seven cases considered. Herxheimer[10] lists metastasis in the following diminishing order of frequency: Lungs and pleura, lymph nodes, bones, epidural space and spinal cord. Uncommon sites are the peritoneum, adrenal, stomach, heart and spleen. Metastasis to the kidney, brain, pancreas and prostate are reported. Mallory[29] speaks of the tumor as one which is

likely to metastasis to bone. Liber and Brown[30] review the various reports of splenic metastasis and conclude that although many tumor cells are seen in the spleen very few true metastases are found there. As observed by Wilbur[22] the multiplicity of intrahepatic metastasis and the sparcity of extrahepatic metastasis suggest a very "individualized" tumor.

Liver cell carcinoma sometimes invades the vena cava. Gregory[31] reviews twelve incidences of tumor thrombosis of the inferior vena cava. The thrombosis has been known to go into the right auricle as well. Obstruction of the portal vein giving splenomegaly is not uncommon in these tumors.

PRIMARY CARCINOMA OF THE LIVER

Case No.	Type	Metastasis	Cirrhosis
1	Liver cell	Lymph nodes	Absent
2	Bile duct	Lymph nodes Heart	Absent
3	Liver cell	Lungs	Present
4	Bile duct	None	Present
5	Liver cell	None	Present

Three of the tumors reported here are metastasized. Two had metastasized to the lymph nodes at the hilus of the liver. One of these had metastasized to the right auricle of the heart as well. In a third metastasis was found in the lungs.

Wilbur[22] reports that three of their forty-nine patients showed enlarged livers. There was an enlargement of the liver in each of our five patients. This varied from an increase of 50 per cent to an increase of 200 per cent in weight.

CASE REPORTS

CASE I. (Unit No. 32387). A male aged fourteen years was admitted to the hospital because of a painful prominent mass in the right upper quadrant. The present illness dated from four months previous to admission. On examination a large mass was found occupying the entire right upper quadrant extending into the epigastrium. A fluid wave was elicited in the abdomen. Laboratory studies revealed the number of erythrocytes to be 3,900,000 per cu. mm.; hemoglobin was 71 per cent (Sahli); leukocyte count 9,750 with 12 lymphocytes, 11 monocytes, 69 segmented forms, 6 basophiles; the icterus index was 22; the van den Bergh reaction was positive direct and indirect 0.8 mg.; cephalin flocculation test was 2 plus in forty-eight hours; prothrombin time was 105 seconds (control 65 seconds); urinalysis showed a trace of albumin with negative reaction for urobilinogen; stool examinations were negative for ova or parasites. Roentgenologic examination was inconclusive.

The patient was acutely ill on admission and his course was rapidly downhill. Severe paroxysms of pain, which were present on admission, became progressively worse and more frequent toward the end. He expired five days after admission.

At autopsy most of the liver substance was replaced by tumor tissue. (Fig. 1.) On microscopic examination this proved to be primary carcinoma of the liver, liver cell type. (Fig. 2.) The only metastases found were in lymph nodes at the hilus. Jaundice was present but there was no cirrhosis. The spleen was enlarged because of the portal obstruction. No ascites was noted at autopsy. The pancreatic ducts were dilated and a few focal areas of recent fat necrosis were present in the peripancreatic fat.

CASE II. (Unit No. 172680). The patient, a white female aged fifty-six years, came under observation one year prior to the final admission because of a genito-urinary infection which rapidly cleared on treatment. There was a past history of two gallbladder operations in 1937, the first for cholecystectomy and two weeks later for removal of a stone in the common duct. After nine months she was again admitted with upper abdominal pain which had gradually increased in severity. These symptoms were now accompanied by anorexia, weakness and loss of weight. Physical examination at this time was essentially negative. The roentgenologic examination of the upper gastrointestinal tract, using a contrast media, was reported as normal. On this admission the patient ran a low grade fever which subsided by lysis and the patient was discharged three weeks later. After two months she was readmitted with practically the same complaint but on this admission she was markedly emaciated. The physical examination, again, was essentially negative although

there was some tenderness in the right upper quadrant and the liver was palpable. The liver border was smooth and non-tender. There was no ascites. There was a low grade fever (100°F.). Laboratory studies revealed the number of erythrocytes to be 3,600,000 per cu. mm.; hemoglobin, 61 per cent (Sahli); leukocyte count, 34,000 with 78 segmented forms, 18 lymphocytes, 4 monocytes; urinalysis showed a trace of albumin; stool examination was negative for bile; Kahn serologic test for syphilis was negative.

The patient complained of constant abdominal pain and was nauseated. An exploratory laparotomy was performed on the thirty-first hospital day. About 350 cc. of dark red peritoneal fluid was removed from the abdominal cavity. There was a large space-occupying mass in the right upper quadrant involving the liver. A biopsy was performed. The postoperative course was stormy and the patient expired five days later.

The pathologic diagnosis from the biopsy was carcinoma, type undetermined. At autopsy the carcinoma was seen to be primary in the liver probably arising from a bile duct in the liver substance. The tumor involved chiefly the right lobe of the liver. It had metastasized into lymph nodes at the hilus of the liver as well as to the right auricle of the heart. There was ascites but no cirrhosis.

Death was due to acute purulent peritonitis.

Case III. (Unit No. 10786.) This seventy-two year old colored male was admitted with the chief complaint of swelling of his abdomen and feet of three weeks' duration. He had been previously treated with digitalis for congestive heart failure and discharged as improved. On this admission his abdomen was markedly distended and was causing respiratory embarrassment. There was a definite fluid wave and shifting dullness. The feet and legs showed a 4 plus pitting edema. A paracentesis was performed and 2,800 cc. of straw-colored fluid was removed. Specific gravity of this fluid was 1.008. Pathologic examination of the fluid for tumor cells was unsatisfactory. The red blood cell count was 3,770,000 with 78 per cent hemoglobin (Sahli). The leukocyte count was 8,000 with 85 per cent segmented forms. The urine was positive for bile; the icterus index was 33 units; van den Bergh reaction was positive direct and the indirect was greater than 8 mg.; the cephalin flocculation test was 4 plus in forty-eight hours. Roentgenologic examination of the lung fields showed some round, soft, well defined infiltration throughout both lung fields.

The patient expired eight days after admission. A primary liver cell carcinoma which had developed in a cirrhotic liver and metastasized to the lungs was found at autopsy. The liver-like cells constituting the tumor were growing in broad sheets. Many of the bile canaliculi and small bile ducts were dilated, probably due to obstruction of these ducts by tumor nodules. Bile casts were found in the kidney tubules. The body was mildly jaundiced. There was marked splenomegaly. Three L. of ascitic fluid were found in the peritoneal cavity.

The only other significant finding was a mild, left cardiac hypertrophy.

Case IV. (Unit No. 27636.) A colored male sixty-one years of age was admitted to the hospital with the chief complaint of massive gastric hemorrhage that had begun approximately at 9 A.M. on the day of admission. Two days previous to onset of hemorrhage he had noted that his stools had been tarry. Two months before his admission to the hospital he had complained of generalized weakness. On examination the sclera showed an icteric tint; the abdomen had a definite fluid wave and shifting dullness. A mass that was continuous with the liver margin could be felt in the right epigastrium. The mass was hard, 2 to 3 cm. in diameter, nodular and non-tender. There was splenomegaly. A diagnosis of primary carcinoma of the liver, superimposed on cirrhosis, was made. No laboratory or roentgenologic examinations were recorded. The patient had repeated bouts of vomiting bright-red blood and expired twelve hours later.

At autopsy a primary adenocarcinoma of the liver was found associated with an old cirrhosis of the liver. The secondary effects associated with the cirrhosis were prominent in the form of splenomegaly, esophageal varices and calcific sclerosis of splenic veins. In fact, it seems that the fatal hemorrhage occurred from a ruptured esophageal varix. The carcinoma had not metastasized.

There was cholangitis together with a few small hepatic abscesses. Other findings were a small amount of lobular pneumonia, benign prostatic hypertrophy, and calcification of the mitral valve ring.

Case V. (Unit No. 12027). A forty-nine year old colored male entered the hospital

complaining of pain in right upper quadrant of four weeks' duration. The pain had steadily increased in severity and occasionally radiated to the right shoulder. There had been a weight loss of 50 pounds and a gradual increasing weakness. On examination the sclera appeared slightly icteric. There was a protuberant mass in the abdomen that was palpable 10 cm. below the right costal margin. The mass was described as smooth and firm and continuous with the edge of the liver. As seen from a lateral view the mass extended above the surrounding level of the abdominal wall. There was a definite fluid wave. Laboratory examination showed the erythrocyte count to be 4,390,000 with 80 per cent hemoglobin (Sahli); total leukocyte count 7,800 with a normal differential ratio; icterus index was 16 units; cephalin flocculation test 3+ (forty-eight hour reading); sickle cell preparation negative; examination of feces for occult blood, ova and parasites was negative. Roentgenologic examination showed an elevated fixed right diaphragm; the gallbladder responded to the dye; contrast media showed no intrinsic lesion in the gastrointestinal tract.

On the twenty-first hospital day an exploratory laparotomy was performed under local anesthesia. The peritoneal cavity was found to contain a moderate amount of blood-tinged ascitic fluid. The liver was seen to be enlarged, nodular, firm and dark red in color. A biopsy was performed. The postoperative course was stormy. The patient expired on the eighth postoperative day.

At autopsy (limited to the abdominal cavity) a primary liver cell carcinoma was found. There was also a diffuse nodular cirrhosis with splenomegaly, jaundice and ascites. No metastases of the tumor were demonstrated.

There was an acute purulent peritonitis which was the probable immediate cause of death.

SUMMARY AND CONCLUSIONS

Five cases of primary carcinoma of the liver have been presented. All cases were proved at autopsy. The recent incidence of primary carcinoma of the liver in our hospital, 1 per cent, is one of the highest reported from the western world. Three of the cases were of the liver cell and two of the bile duct type. Cirrhosis was present in three of the five cases.

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Primary Carcinoma of the Liver*

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THE rarity of primary carcinoma of the liver in Europe and North America and the difficulty in establishing diagnostic criteria for this condition have prompted us to make a study of the various patients seen at autopsy and operation at the Jewish Hospital of Brooklyn.

TABLE I

Spatt and Grayzel	Pack and Lefevre[11]	Wilbur et al.[15]	Gnassi[8]	Loesch[10]	Gustafson[5]	Charache[5]
0.23%	0.17%	0.44%	0.14%	0.46%	0.26%	0.56%

A series of seventeen cases of primary carcinoma of the liver is presented of which eleven have come to autopsy. Of a total of 4,731 postmortem studies done at this hospital up to July, 1946 eleven autopsied cases of primary carcinoma of the liver were seen (0.23 per cent). For comparison with the incidence in other series see Table I.

It is well known that the incidence of this lesion is much higher among Asiatics than it is among those of Europe and America. For example, Berman[2] gave the percentage of primary carcinoma of the liver in all autopsies as 1.3 per cent for Javanese, 1.21 per cent for Japanese and 1.2 per cent for the Bantu tribes of Africa.

Of the eleven autopsied cases, nine were adults and two were children. The latter were four months and one year and four months old, respectively. Of the nine adults who came to necropsy, seven (78 per cent) had accompanying portal cirrhosis in the portion of the liver uninvolved by the tumor. This compares with 54 per cent in the series of Wilbur et al.[15] This latter figure is much lower than is found in most other series, i.e., Loesch[9] 86 per cent, and Greene[7] who, in 386 cases gleaned from the literature, found the percentage of cirrhosis in hepatocellular carcinomas to be 87 per cent. Strong and Pitts[12] found that in ten cases in Chinese people, 100 per cent had cirrhosis of the liver. Tull[13] stated that cirrhosis was present in the great majority of cases, especially those of the liver cell type. Brines[4] stated that a much higher percentage of primary carcinoma of the liver is apparently found in autopsies on patients in whom chronic liver diseases are present. The aforementioned statements and figures indicate that chronic liver disease plays some etiologic rôle in carcinoma of the liver, or that a common etiologic factor may be involved in both conditions. Of the eleven cases which came to necropsy, 9 (82 per cent) showed extrahepatic metastases. (See Table II for the location of metastases and a comparison with other series.)

TABLE II

Location of Metastases	Spatt and Grayzel, Per cent	Wilbur et al.	Loesch	Gustafson	Greene
Lungs	67	second most common	second most common	second most common	
Tumor thrombi in veins	44	.....	most common		
Omentum	33				
Bones	22				
Regional lymph nodes	22	most common site	.....	most common site	most common site
Suprarenal glands	22				
Pancreas	11				

Extrahepatic metastases occurred in six of seven hepatocellular (86 per cent), in two of three cholangiocellular lesions and in

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one undetermined cellular type. Of the present series of seventeen cases ten (59 per cent) were hepatocellular, five (29 per cent) were cholangiocellular and two (12 per cent) were of undetermined origin. (For comparison with other series see Table III.)

Primary carcinoma of the liver is obviously a disease which preponderantly affects males. There is no significant history of alcohol in our patients to account for the difference in incidence between males and females. The greater incidence in males may be at least partially accounted for by the greater frequency of cirrhosis of the liver in males. Certainly, the two conditions, cirrhosis and carcinoma of the liver, occur together very frequently.

TABLE III

	Spatt and Grayzel, Per cent	Wilbur et al., Per cent	Loesch, Per cent	Gustafson, Per cent	Greene	Strong and Pitts, Per cent	Tull
Hepatocellular	59*	92	86	63	"Liver cell carcinoma far outnumbered duct cell carcinomas"	67	"Liver cell type is nearly 3 × as common as the bile duct type"
Cholangiocellular	29	8	..	..			
Undetermined	12	..	..	..			

* If the two cases of undetermined type of carcinoma were to be added to the hepatocellular group, the percentage (71 per cent) would more nearly approximate those of most other workers.

TABLE IV

Age	Spatt and Grayzel, Per cent	Wilbur et al.	Loesch	Gustafson	Greene	Upham and Klotz[14]
45–54	27	Most cases between 41 and 70 years fairly well distributed in the three decades between 41 to 70	.....	Highest incidence in fifth, sixth and seventh decades	Greatest incidence 50 to 59 years	Greatest incidence between 40 and 60 years
55–64	46					
65 and over	27					
Average age	60 years	.....	59.5 years	52.5 years		

The youngest patient in our series was four months old; the oldest was seventy-three years old. There was no significant difference in the ages of the males and females. (See Table IV for comparison with other series.)

The ratio of males to females in the authors' cases was 65 per cent males and 35 per cent females. (For comparative figures see Table V.)

TABLE V

	Spatt and Grayzel	Wilbur et al.	Loesch	Gustafson	Greene
Males (per cent)	65	86	86	85	86
Females (per cent)	35	14	14	15	14

CLINICAL DATA

The length of the clinical course in this series varied from one to twelve months with an average of three and three-fourths months. In 86 per cent of the cases it was less than five months. The short clinical course is similar to that found by most other workers in the field. In fact, Upham and Klotz[14] and Morehead[10] maintained that patients with untreated carcinoma of the liver never survive more than four months.

(For the most consistent signs and symptoms see Table VI.)

Thus the signs and symptoms are seen to be non-specific so that this diagnosis is a very difficult one to make clinically. As Boyce and Mcfetridge[3] put it, "The clinical course is absolutely atypical and diagnosis is rarely made antemortem except in those localities in which the disease is relatively frequent."

TABLE VI

Signs and Symptons	Percentage of Cases in Which Signs and Symptoms Were Present
Rapidly enlarging abdominal mass	88
Abdominal pain	82
Sustained temperature of over 100°F.	64
Marked weight loss	53
Severe anorexia	47
Nausea and vomiting	47
Constipation	47
Icterus	47
Ascites over 1,000 cc	35*

* In 50 per cent of these the fluid was bloody.

The diagnosis was made clinically in the authors' series in only 6 per cent of the cases. The remainder of the patients were diagnosed only after operation or post-mortem examination. The diagnosis made in most of the patients was either "cirrhosis of the liver" or "carcinoma, metastatic, in liver." Difficulty in diagnosis was noted by all the workers in this field except those in South Africa and Asia where the disease occurs fairly frequently. The importance of early diagnosis is perhaps not too great at present since little can be done in the way of treatment. However, some authors[1,5,14] recommend surgical extirpation of the tumor as a treatment offering some hope. In fact, Charache[5] mentions one case of a nine-year cure after surgery. On the other hand, surgery is thought to be of doubtful value by others.[2,7]

LABORATORY DATA

The icterus index varied from 8.4 to 380.4 in nine patients. The average value was 84.1. There were only two values below 10 and there were six values above 40, so that the icterus index was high fairly consistently in this series. In fourteen patients, the blood sugar varied from 73 to 153 mg. per cent. The average value was 108 mg. per cent. Thus it may be seen that there was no significant variation in the blood sugar from the normal in these patients.

TABLE VII*

Case I	15 per cent dye retained after thirty minutes
Case II	20 per cent dye retained after thirty minutes
Case III	30 per cent dye retained after thirty minutes
Case IV	90 per cent dye retained after thirty minutes

* 5 mg. of dye/Kg. of body weight given.

The alkaline phosphatase value varied from 6.1 mg. per cent to 28.3 mg. per cent (Bodansky units); the average value was 16.9 mg. per cent. Of seven patients in whom this test was recorded, all were above the normal value. In five patients the values were above 19 mg. per cent; in only one of these were there metastases to bone. Therefore, it may be said that the alkaline phosphatase is usually high in primary carcinoma of the liver. The serum protein value varied between 5.7 and 6.9 Gm. per cent so that there was no significant change.

The total blood cholesterol in seven patients varied from 159 mg. per cent to 352 mg. per cent. Normal values in this institution are 150 to 280 mg. per cent. The total cholesterol values were above the upper limits of normal in only two cases. The percentage of free cholesterol was higher than the upper limits of normal in three patients, the extreme being 85.4 per cent (normal 22 to 28 per cent). Thus the cholesterol values were not significant in this group of patients. The cephalin flocculation test was recorded in six patients and varied from negative to 3+. It did not yield consistent results in this series. In four cases the bromsulfalein test was done, with results as seen in Table VII.

Thus these test values consistently indicated liver damage. Their significance is limited only by the small number of bromsulfalein tests done. In thirteen patients in whom the red blood cell count was recorded the extremes were 1,450,000 and 4,800,000 and the average was 3,700,000. Severe anemia did not occur frequently.

SUMMARY AND CONCLUSIONS

1. A series of seventeen cases of primary carcinoma of the liver has been studied and the literature reviewed.

2. The rarity of the lesion in this area was confirmed (0.23 per cent of all autopsies).

3. There was some indication that cirrhosis of the liver plays a rôle in the etiology of this disease, or that some etiologic factor is common to both.

4. Extrahepatic metastases were present in 82 per cent of the patients.

5. Hepatocellular lesions far outnumbered those of cholangiocellular origin.

6. The age incidence varied from four months to seventy-three years, almost one-half the cases occurring between fifty-five to sixty-four years.

7. Males predominated over females (2:1).

8. The length of the clinical course was short, averaging three and three-fourths months.

9. The most consistent signs and symptoms were (1) rapidly enlarging abdominal mass, (2) abdominal pain, (3) sustained temperature over 100°F., (4) marked weight loss. Anorexia, nausea and vomiting, constipation, icterus and ascites were less frequent.

10. Diagnosis is difficult and infrequently made clinically.

11. The most consistent liver function tests were (1) icterus index, (2) alkaline phosphatase, (3) bromsulfalein test. The blood sugar, serum protein, cholesterol, cephalin flocculation test and red blood cell counts were not significant.

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Review

So-called Extrarenal Uremia*

A Study of Twenty Cases

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DURING Bright's time and until recently uremia was considered one of the chief syndromes of renal insufficiency brought about by nephritis, obstructive uropathies or some other organic disease of the kidney. The occurrence of uremia in the absence of demonstrable and significant renal lesions, however, is an unexpected event more frequent than it is thought to be and which is often overlooked. This condition was not recognized until the year 1912 when Froin and Marie[1] and Nobécourt, Bidot and Maillet[2] observed this clinical syndrome in patients suffering with cholera and diarrhea in infancy. Tileston and Comfort[3] in 1914 in an investigation of azotemia of non-renal origin gave a more comprehensive description of the disorder.

Since that time, many articles[4–15] have described extrarenal uremia, and the conditions held responsible for this syndrome have been numerous and varied. Intestinal obstruction, hepatitis, diabetes, myocardial infarction, Addison's disease, shock, burns and hemorrhage are a few conditions often associated with it. But almost any serious illness or injury may be looked upon as a cause of extrarenal uremia. A puzzling question is whether or not, in all of these cases, there is a common factor accountable for the extrarenal uremia. So far there is no satisfactory answer.

Since extrarenal uremia (prerenal uremia, non-renal azotemia) occurs in association with some primary serious disorder, its features may be confused with signs and symptoms of the original disease. As extrarenal uremia is a clinical syndrome its features are not always the same. However, some of the chief characteristics are uniformly present despite the diverse nature of the primary disorder responsible for it. Dehydration, stupor, azotemia, low blood pressure and a shock-like appearance are practically always found. In some cases alkalosis and hypochloremia are present and in others acidosis and normal chloridemia exist.

Considerable dissatisfaction has arisen over the use of the term extrarenal uremia. Prerenal azotemia and non-renal azotemia have been substituted for it.[19,25] The chief fault found with the term extrarenal uremia is that it fails to differentiate the azotemias due to obstructive uropathies from the nitrogen retention of metabolic origin. The terms extrarenal uremia and extrarenal azotemia are frequently used interchangeably. This is not quite correct for extrarenal azotemia indicates merely a retention of nitrogenous substances in the blood which depend upon factors operating in the absence of primary renal impairment. Extrarenal uremia, on the other hand, is a symptom complex in which azotemia is always present, but there are other signs and symptoms which characterize it, such as stupor, delirium, twitching and a shock-like appearance. However, use of the term uremia has become fairly well entrenched in the literature and until a more appropriate term becomes established we believe it is wise to adhere to it. It should be kept

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in mind that the term extrarenal uremia indicates that the chief factors responsible for it occur outside of the kidney, such as shock, dehydration and vomiting. Nevertheless, extrarenal uremia which ensues is a result of renal insufficiency even though functional in nature. Regarded in this light the term extrarenal uremia is a misnomer, and the older generation of clinicians may have been correct in holding the opinion that all uremia emanates from disordered kidneys. There is one prominent difference between the common type of genuine uremia and the kind under discussion here: that is the absence of organic changes in the kidney other than those usually found in the kidneys of patients dying from any long illness without disease of the kidney. In the study of eighty-four cases of extrarenal azotemia Bell and Knutson[16] found mild to severe hydropic degeneration of the proximal convoluted tubules in twenty, indicating that tubular injury may have been, in part, or entirely responsible for the uremia. In the remaining sixty-four there were no structural changes in the kidney. As they point out it is difficult to make a sharp differentiation between true extrarenal azotemia and azotemia due to tubular injury. So-called extrarenal uremia is a functional disease of the kidney which is the result of one or more disorders occurring outside of the kidney. It is still necessary, however, to give consideration to the mechanisms which diminish renal function and produce so-called functional or extrarenal uremia.

The purpose of this report is threefold: (1) To present a group of twenty cases illustrating extrarenal uremia and the varied types of primary diseases which may be responsible for it. (2) To emphasize the importance of recognizing this syndrome early because if the proper diagnosis is made rational treatment is followed by gratifying results. (3) To emphasize the need for further investigation of the kidney in extrarenal uremia, with special attention to the tubules and the recent work of Trueta et al.[17]

In Table I is a summary of the twenty cases which were selected to illustrate the clinical, chemical and pathologic features of this disorder. The cases are arranged according to the primary disorder considered to be the cause of extrarenal uremia. Cases I to IX resulted from gastrointestinal disorders. Cases X to XIII were associated with hepatitis or some form of liver disease. Cases XIV and XV followed infection and Cases XVI and XVII were examples of vasomotor disturbances associated with heart failure due to coronary artery disease; the brain and peripheral nervous system were involved in Cases XVIII to XX.

In all the patients in the gastrointestinal group there was excessive vomiting, dehydration and pain in the upper abdomen. One patient had marked diarrhea with associated acidosis, six had alkalosis and three had acidosis. There was a previous ulcer history in four of the nine patients and three of the four had suffered perforation. Oliguria and hemoconcentration were present in all nine patients. In three of the nine evidence of tetany was present on first examination. In one patient there were cramps of the hands and feet for two months prior to the onset of symptoms of his last admission. Four of the patients showed symptoms of delirium, stupor or hyperactivity and this we believe constituted evidence of uremia as differentiated from simple azotemia. Six of the nine patients recovered with appropriate treatment which was aimed primarily at restoring the fluid and electrolyte balance as well as correcting mechanical obstructions present by surgical measures. During the course in the hospital one patient (Case IV) showed evidences of some structural damage of the kidney. After death and at autopsy this was borne out by the finding of distinct changes in the tubular epithelium of the proximal and distal convoluted tubules. The epithelial cells were swollen and showed granular dehydration throughout. The glomeruli were intact, and there were arteriosclerotic changes in the medium-sized and smaller

TABLE 1

SUMMARY OF CASES

Case Age Sex	Admittance Date	History	Examination	Blood Pressure	Urinalysis	Blood Chemistry	Laboratory Data	Treatment	Remarks
I 37 w/m	2/15/46	Ruptured gastric ulcer Upper abdominal pain Vomiting Weakness Weight loss	T. 97.8°F. P. 76 R. 18 Restless Hiccoughs Dehydrated Abdominal tenderness	140/80	Sp. gr., 1.004 to 1.012 Alb. 0 Sugar 0 Later: Alb. 2+ R.B.C. occasional W.B.C. occasional casts 1 to 2 (hyaline)	N.P.N. 137.8 NaCl 200 CO_2 97.0 Sugar 148.2	Addis count R.B.C. 4,906,543 W.B.C. 19,631,258	Penicillin 4,000 cc. glucose + saline Gastric aspirations up to 900 cc. Gastrojejunostomy	Operative findings: Prepyloric cicatrix producing almost complete obstruction Numerous adhesions between liver and first part of duodenum and anterior aspect of pancreas Discharged, improved
II 52 w/m	5/10/44	Vomiting 5 mo. Persistent peptic subphrenic abscess Congenital kidney disease	T. 98.6°F. P. 88 R. 24 Irrational Dehydrated Muscular twitchings Positive Trousseau and Chvostek signs Abdomen rigid with hypoactive B.S.	140/90	Sp. gr. 1.011 Alb. 3+ R.B.C. 0 W.B.C. many Casts 0	N.P.N. 97.7 NaCl 240 CO_2 87.0 Normal on 10th postoperative day	W.B.C. 17,000 Gastric retention at 4 hr.	Wangensteen suction 4–6,000 L. n/saline Postgastroenterostomy	Dense adhesions above liver, duodenum and pylorus Discharged as improved 31st hospital day
III 52 w/m	8/15/42	Epigastric pain Vomiting Cholecystectomy for gallbladder empyema 2 yr. prior to entry	T. 100.6°F. P. 100 R. 28 Sluggish Dehydrated Enlarged liver Jaundice	105/65	Sp. gr. 1.016 Alb. 3+ Sugar 0 R.B.C. 0 W.B.C. 0 Casts 0	N.P.N. 104 NaCl 260 CO_2 40.0	Cholesterol 132 Icteric Index 45	Wangensteen suction 6,000 cc. parenteral fluids	Expired No postmortem
IV 56 w/m	2/21/42	Nausea 1 mo. Vomiting Repair of perforated peptic ulcer Occasional pain Urinalysis negative on previous admission	T. 96.4°F. P. 118 R. 26 Dehydrated Soft abdomen with marked tenderness Confused Disorientated	105/85	Sp. gr. 1.012 Alb. + Sugar 0 R.B.C. 2 W.B.C. 4 Casts occasional	N.P.N. 226.5 NaCl 340 CO_2 78.0	.....	4,000 cc. glucose in saline	Expired 11th day Gastric ulcer Pyloric stenosis Interstitial renal edema and tubular degeneration
V 48 w/f	4/23/46	Vomiting Nausea Cramps of hands and toes Previous gastric ulcer Oliguria for 5 days	T. 99.8°F. P. 108 R. 12 Weak pulse Respirations shallow Epigastric tenderness Distention	106/70	Sp. gr. 1.010 Alb. 3+ Sugar 0 R.B.C. 5–10 W.B.C. 15–20 Casts 0	N.P.N. 150.8 NaCl 260 CO_2 65.5	W.B.C. 8,800 Hgb. 94%	Intravenous calcium gluconate 5,000 cc. saline intravenously	Improved Discharged 4/27/46
VI 28 w/f	5/19/46	Nausea Vomiting Rectovaginal fistula and abscess Chronic ulcer Colitis Profuse exudate from distal loop of ileostomy	T. 98°F. P. 140 R. 30 Ileostomy with drainage of rectovaginal fistula and abscess Marked emaciation Weakness Pallor	110/70	Sp. gr. 1.015 Alb. 0 Sugar 0 R.B.C. 0 W.B.C. occasional Casts 0	N.P.N. 82.5 NaCl 280 CO_2 84.8	Sed. rate 32/63 W.B.C. 50,600 Hgb. 95.5%	Plasma Saline Wangensteen suction External heat Blood transfusion	Improved after 12 hr.

TABLE I.—(*Continued*)

Case Age Sex	Admittance Date	History	Examination	Blood Pressure	Urinalysis	Blood Chemistry	Laboratory Data	Treatment	Remarks
VII 22 w/f	2/4/46	Vomiting Diarrhea Abdominal cramps Irrational	T. 101°F. P. 110 R. 16 Physical findings essentially negative	122/82	Sp. gr. 1.010 Alb. 2+ Sugar 0 R.B.C. occasional W.B.C. few Casts occasional Amt. 400–800 a day	N.P.N. 132 NaCl 375 CO_2 30 Normal after parenteral saline	Lungs normal Gastrointestinal series negative W.B.C. 18,500 Blood cholesterol 210	Normal saline 3,000/d for 3 days	Recovery in about 2 wk. Stuporous, irritable and partially irrational response with clinical improvement on 3rd day
VIII 26 w/f	11/3/46	Vomiting Nausea Nocturia Pregnant 4 mo.	T. 98°F. P. 110 R. 26 Distended small bowel Tender	84/60	Alb. 2+ Sugar 0 W.B.C. occasional R.B.C. 0 Oliguria	N.P.N. 125 NaCl 313 CO_2 67	Obstruction in duodenum Pregnant 4 mo.	Removal of obstruction Meckel's diverticulum	Recovery
IX 74 w/f	10/7/45	Epigastric pain Nausea Vomiting	T. 100°F. P. 80 R. 20 Tender abdomen	104/60	Oliguria negative	N.P.N. 157.6 NaCl 360.0 CO_2 42.8	Hgb. 88% W.B.C. 10,500 Sed rate 102/110	Wangensteen suction Penicillin Oxygen Plasma Fluids	Expired 19 hr. after admission
X 64 w/m	4/26/46	Weakness Jaundice Ankle edema Abdominal pain Weight loss Anorexia Dysuria Alcoholism	T. 96.4°F. P. 120 R. 26 Confused Dehydrated Hemorrhages of the soft palate Abdomen tense Liver enlarged and tender Jaundice	90/48	Alb. 1+ Sugar 0 R.B.C. 0 W.B.C. 0 Casts 0 Bile +	N.P.N. 200.0 NaCl 440 CO_2 52	Kline negative R.B.C. 3.23 W.B.C. 18,650 Hgb. 81% Icteric Index 94.8 Bleeding time prolonged over 24 minutes	Antispasmodics Alkalinization Intravenous fluids Vitamin C Sedation Wangensteen suction Amigen Liver extract Synkamin Intraheptol	Expired 4/30/46 Cholemia Hepatitis, non-specific Nephrosis, cholemic and sulfonamide Coronary and renal arteriosclerosis with myocardial fibrosis Cerebral edema with focal encephalomalacia
XI 28 w/m	1/5/44	Inability to void for 48 hr. Edema Abdomen distended Jaundice	T. 98.8°F. P. 90 R. 20 Enlarged heart Edematous Hydration adequate	124/60	Sp. gr. 1.015 Alb. 3+ Sugar 0 R.B.C. 0 W.B.C. 0 Casts 2+ granular	N.P.N. 95.2 NaCl 400 CO_2 27.7	W.B.C. 17,500 Hgb. 15.5% Blood culture negative	Glucose and sodium lactate Intravenous solutions	Expired 1/11/44 Uremia Cirrhosis of the liver Anasarca Congested kidney
XII 28 w/m	9/30/43	Confused Weakness Alcoholism Weight loss	T. 96.4°F. P. 119 R. 23 Irrational Dehydrated Liver enlarged	116/84	Sp. gr. 1.017 Alb. 0 Sugar 0 R.B.C. 0 W.B.C. occasional Casts 0 Oliguria	N.P.N. 130 CO_2 23.0	Chest x-ray negative Sed. rate rapid	Oxygen 3,000 cc. glucose + saline Intravenous calcium gluconate	Expired 10/18/43 No postmortem
XIII 54 w/m	4/17/46	Dyspepsia Hematemesis Jaundice	T. 101.2°F. P. 110 R. 30 Liver enlarged 1+ edema of legs	138/70	Sp. gr. 1.021 Alb. 0 Sugar 0 R.B.C. 0 W.B.C. 0 Casts few	N.P.N. 41.3 NaCl 302 CO_2 38.0	R.B.C. 2,300,000 W.B.C. 5,200 Hgb. 50.5% Examination of lungs negative	Sedation 2,500 cc. Blood transfusion 2,000 cc. 5% glucose/d Sodium lactate	Expired 4/22/46 Hepatic portal cirrhosis esophageal varices Icterus Renal congestion
XIV 55 w/f	3/25/44	Vomiting Epigastric pain Weakness Numbness Weight loss Oliguria Thirst	T. 97°F. P. 120 R. 30 Dehydrated	90/60	Sp. gr. 1.014 Alb. 0 Sugar 0 R.B.C. 0 W.B.C. 10.20 Casts 0 Oliguria	N.P.N. 88.4 NaCl 586 CO_2 27.7 Sugar 286	.....	Sedation Fluids	Expired 3/27/44 Pulmonary tuberculosis Tubercular bronchiectasis of left apex Tubercles of left lower lung Tubercular enterocolitis Myocardial degeneration Cerebral edema

TABLE I.—(*Continued*)

Case Age Sex	Admittance Date	History	Examination	Blood Pressure	Urinalysis	Blood Chemistry	Laboratory Data	Treatment	Remarks
XV 61 w/m	10/2/31	Pain in left chest Chills Fever Sweating	T. 102.8°F. P. 120 R. 32 Consolidation of left chest Tachycardia	118/84	Sp. gr. 1.012 Urine negative Later: Alb. 1–2+ R.B.C. 4 W.B.C. 8–10 Casts occasional granular	N.P.N. 94 CO_2 45	Left hydrothorax Consolidation of left lung	Aspiration Rib resection with drainage Intravenous fluids	Recovery 2 wk. Oliguria during hospital stay
XVI 51 w/m	5/7/46	Substernal pain Shock Vomiting Dyspnea Alcoholism	T. 100.6°F. P. 120 R. 40 Restless Enlarged liver Cyanosis of lips and nail beds	98/70	Sp. gr. 1.016 Alb. 0 Sugar 0 R.B.C. 0 W.B.C. 0 Casts 0	N.P.N. 120 NaCl 310 CO_2 42	ECG showed myocardial infarction of anterior wall W.B.C. 31,400 Hgb. 101%	Oxygen Pantopan Plasma Atropine Quinidine Whiskey	Expired 4th hospital day No autopsy
XVII 54 w/m	2/28/44	Epigastric pain Nausea Vomiting Tachycardia	T. 97°F. P. 120 R. 26 Auricular fibrillation Epigastric tenderness Irrational	88/62	Sp. gr. 1.012 Alb. 0 Casts few Oliguria	N.P.N. 72 NaCl 273 CO_2 78	Hiatus hernia Auricular fibrillation	Intravenous NaCl and glucose 4,000 cc. intravenously	Full recovery on 10th day
XVIII 54 w/m	9/12/45	Vomiting 3 weeks	T. 100°F. P. 90 R. 24 Bitemporal hemianopsia Positive Hoffmann's sign bilaterally Weakness of right side of face Tongue deviated to right	160/100	Sp. gr. 1.015 Alb. trace W.B.C. occasional R.B.C. 0	N.P.N. 108 NaCl 627 CO_2 32	Skull x-ray revealed erosion of posterior clinoids	Surgery Intravenous glucose	Azotemia corrected Patient died following surgery Chromophobe adenoma of pituitary
XIX 51 w/f	4/4/46	Psychosis-mania hyperactivity Semistuporous	T. 107.6°F. P. 120 R. 27 Bigeminal pulse Skin cool and moist Cyanotic	Unobtainable	Sp. gr. 1.008 Alb. + Sugar 0 R.B.C rare W.B.C. 5–10 Casts rare	N.P.N. 128 NaCl 295 CO_2 62	Spinal fluid negative Kline negative	Oxygen Plasma 600 cc. Parenteral glucose and saline 3,000 cc.	Lapsed into coma Expired after 20 hr. in hospital
XX 33 c/m	3/26/46	Fever Hyperactivity Psychosis Catatonia	T. 101.2°F. P. 130 R. 27 Restless Muttering Frequent bowel movements Mucous membranes dehydrated	110/70	Sp. gr. 1.006 Alb. 0 Sugar 0 R.B.C. 0 W.B.C. 0 Casts 0	N.P.N. 110.8 NaCl 270 CO_2 84	Spinal puncture negative W.B.C. 15,200 Hgb. 88% X-ray of chest negative	Parenteral fluids Glucose and saline up to 3,000 cc. daily Penicillin	Improved Discharged 4/22/46 No cause for fever found

arteries of the kidney but not of an advanced degree.

The following is an illustrative case of the gastrointestinal group. This patient vomited as the result of pyloric obstruction which developed subsequent to an old perforated gastric ulcer. It also shows the effectiveness of treatment in this type of case.

CASE REPORTS

CASE I. F. L., a thirty-seven year old white male, was admitted on February 15, 1946. For a

period of three days the patient had severe epigastric pain with marked vomiting, followed by stupor two hours prior to admission. He suffered a ruptured gastric ulcer nine years previously and was operated upon at that time. A few months following this he experienced postprandial pain. During the eleven months prior to the last admission he suffered repeated episodes of vomiting, weight loss and cramping of the hands and feet with marked paresthesia. Consumption of large quantities of baking soda was the only means of relief. Examination on entrance revealed a well developed, undernourished, stuporous white male, with marked pigmentation of the skin. Pulse was 76; respirations, 18; temperature, 97.8°F. and blood pressure 140/80. He was irritable, hiccoughed continuously and his tongue was very dry. The sclerae were clear and the fundi were normal. These was a negative Chvostek's sign. Examination of the chest, lungs and heart disclosed no abnormalities. There was an epigastric scar. There were no abdominal masses; the gurgles were normal and no distention or rigidity were found. The entrance impressions were coma due to Addison's disease, drug intoxication or possibly uremia. Laboratory tests showed a non-protein nitrogen of 137.8 mg. per cent and an alkali reserve of 97 volumes per cent. The urinalysis was negative for albumin, sugar and formed elements. The blood disclosed the following: hemoglobin, 97 per cent; white blood cells, 27,550; bands, 35 per cent; polymorphonuclears, 55 per cent; lymphocytes, 4 per cent and monocytes, 6 per cent. On the first hospital day the patient had a convulsion which lasted several minutes; this was controlled with intravenous sodium amytal.

Treatment included parenteral glucose and saline in amounts ranging from 4 to 6 L. a day. Adrenal cortical extract and penicillin were administered during the first two hospital days. By the third day the patient was improved and the temperature which had developed after entrance had fallen to normal. By the seventh day the non-protein nitrogen had fallen to 50 mg. per cent and the sodium chloride of the blood had risen from 200 mg. per cent to 440 mg. per cent. There was a gradual fall of the alkali reserve from a high upon entrance of 97 volumes per cent to 65 volumes per cent. On the tenth hospital day the urine showed no albumin, no sugar, 2 to 3 red blood cells per high power field and 7 to 12 white blood cells. There were a few hyaline casts in the urinary sediment. Renal function studies carried out twenty-one days after admission revealed a urea clearance of 33.3 per cent of normal. A repeat examination ten days later revealed a urea clearance of 33.3 per cent of normal. The Volhard test showed concentrations varying from 1.005 to 1.018 on the first examination and 1.008 to 1.016 on the second examination. The Addis count performed on the eleventh hospital day showed 4,900,000 red blood cells, 19,600,000 white blood cells and 46,000 hyaline casts. This was repeated on the eighteenth hospital day and the red blood cells numbered 25,000,000 and the white blood cells numbered 339,000,000. A gastrojejunostomy was performed on the thirty-third day. At operation a large cicatrix at the pyloric area with almost complete obstruction and associated adhesions between the level of the first part of the duodenum and the anterior aspect of the pancreas was found. Two days postoperatively the non-protein nitrogen of the blood had again risen to 103 mg. per cent; the chlorides had fallen to 240 mg. per cent and the alkali reserve had risen to 96 volumes per cent. Change in the blood chemistry developed in spite of adequate pre- and postoperative care. The rise in alkali reserve may have been due to a low reserve type of kidney which was unable to withstand the shock imposed upon it by the surgical procedure. Following surgery, his progress was satisfactory. The blood chemistry returned to normal levels and he was symptomatically much improved. The patient left the hospital against advice ten days after the operation.

Four cases (Cases X to XIII) may be classified fundamentally as diseases of the liver. Three had jaundice and symptoms of the hepatorenal syndrome. In two cases a history of alcoholism was obtained. Prior to entrance one had hematemesis from a ruptured esophageal varix.

The following is a case demonstrating the rôle of severe liver disease in producing extrarenal azotemia:

CASE X. F. H., a sixty-four year old white male, was admitted April 26, 1946. He had been getting progressively weaker for several months and had been unable to work; he had noticed ankle edema for a period of two weeks prior to admission. He admitted some weight loss. There

was no history of clay-colored stools, but his urine had been dark for about one week and visible jaundice had appeared a day prior to entry. The past medical history was non-contributory. He admitted moderate drinking. Physical examination revealed a well developed, well nourished, extremely jaundiced, acutely ill, cooperative but mentally confused white male. The sclerae were icteric and injected; funduscopic examination revealed normal fundi. The mucous membranes were dry and there was a small hemorrhage in the soft palate. There were no abnormal neck masses or pulsations. The lungs revealed no abnormalities. The heart was not enlarged; there was an occasional ectopic beat and the rate was 80 and the blood pressure was 80/48. The abdomen had several small telangiectatic spots in the skin; it was held tense and there was moderate generalized tenderness. The liver was tender and enlarged to 4 finger breadths below the costal margin. The spleen was not palpable and no other masses were felt. There was a 1 plus pitting edema of the extremities. The genitalia were normal. Rectal examination revealed no abnormal masses. The prostate was normal; neurologic examination revealed physiologic reflexes.

Laboratory examination revealed the following: Urinalysis 1 plus albumin, no sugar, no red blood cells and no white blood cells. Blood: red blood cells, 3,230,000; hemoglobin, 81 per cent; white blood cells, 18,650; bands, 20 per cent; segments, 68 per cent; metamyelocytes, 2 per cent; monocytes, 4 per cent and lymphocytes, 6 per cent. Blood chemistry: non-protein nitrogen, 200 mg. per cent; sugar, 53.3; creatinine, 6.0; NaCl 440. Serology: Wassermann and Kline, negative. Galactose tolerance: normal. X-ray of chest was negative with the exception of an old fractured clavicle on the right side. The heart and lungs were within normal limits. X-ray of the abdomen: The liver appeared enlarged; the kidneys were normal in size, shape and position. ECG was within normal limits.

Treatment consisted of intravenous glucose and saline, a high carbohydrate, high protein and liquid diet, vitamin K and liver extract intramuscularly and amigen intravenously daily. He became progressively worse and delirium increased. Later he developed twitchings of small muscle groups; the pulse became weak and thready and he expired April 30, 1946, five days after admission.

The following case (Case xv) is one of azotemia in a patient with empyema as a result of pneumonia in the absence of structural renal damage. Dehydration and tissue destruction were prominent as evidenced by the high fever and oliguria. The urine was normal at the time of entrance to the hospital and, subsequently, there was no evidence of renal insufficiency. Albumin, red blood cells and white blood cells were found in the urine during the course of the illness but the urine was normal at discharge.

Case xv. This patient, a white male laborer sixty-one years of age, was admitted October 2, 1931, complaining of pain in the left chest, chills and fever for several days prior to admission. On physical examination the patient was found to be a well developed, well nourished male, acutely ill. His temperature was 102.8°F., pulse 120 and blood pressure 118/84. Examination of the chest showed consolidation on the left side with typical findings of acute lobar pneumonia. Eight days following admission he became stuporous. Examination revealed an accumulation of fluid in the left chest. Chemical examination of the blood showed a non-protein nitrogen of 94 mg. per cent and creatinine of 3.2 mg. per cent. Urinalysis on admission was essentially negative. Repeated urinalyses at the time the non-protein nitrogen was elevated showed that the patient had a trace of albumin and a few pus cells in his urine. The white blood cell count was 19,500. Hemoglobin and red blood cells were within normal limits. On October 18th the patient had unmistakable signs of empyema involving the left hemothorax. At this time the non-protein nitrogen was 124 mg. per cent and blood creatinine was 4.4 mg. per cent. The urine revealed 2 plus albumin, 8 to 10 pus cells per high power field and 3 to 4 red blood cells per high power field. A few granular casts were found. Three weeks after onset of the illness the left chest was aspirated and fairly thick pus was removed. Two days later a rib resection was done and adequate drainage of the empyema was established. The temperature dropped

to normal, the pulse rate came down to 84 and the non-protein nitrogen which had previously been high returned to normal. The urinary output rose from 500 cc. per day to 1,500 cc. per day. The patient made an uneventful recovery.

A patient (Case XVI) who was studied illustrated extrarenal uremia caused by altered circulation due to coronary occlusion.

CASE XVI. F. P., a fifty-one year old white male, was admitted May 7, 1946, complaining of severe substernal pain, vomiting and mild dyspnea. Illness began two days prior to admission when he was stricken with a substernal pain which travelled from the sternum into the muscles of the arms and shoulders and was accompanied by sweating and vomiting. The patient was a well developed, well nourished male with a temperature of 100.6°F., blood pressure of 98/70 and a pulse of 120. The nail beds and lips were cyanotic; the heart sounds were distinct and of poor quality; no enlargement or murmurs were found. There were moist râles in both bases of the lungs. The liver was enlarged 4 finger breadths below the costal margin and was non-tender. The patient was given pantopon, papaverine and atropine upon admission. Stimulants were administered as well as adrenal cortical extract. The next day orthopnea was less marked but slight pain in the chest persisted and the patient appeared critically ill. His pulse remained rapid and the congestion in his lungs increased. Two days after admission he was dyspneic, slightly confused and restless and complained of pain in the epigastrium. Cyanosis was present, the heart tones were not audible and the pulse was rapid and thready. By the fourth day the patient was more confused, the blood pressure was 70/65, a gallop rhythm was heard, the pulse rate was 110 and the pulmonary congestion increased. He expired on that hospital day.

Laboratory work revealed the following: ECG showed evidence of an anterior wall infarction. Urinalysis: specific gravity, 1.016; microscopic, essentially normal. Blood: white blood cells, 31,400; hemoglobin, 101 per cent; band forms, 20 per cent; polymorphonuclears 63 per cent; monocytes, 2 per cent; lymphocytes, 15 per cent. Non-protein nitrogen, 120 mg. per cent; sedimentation rate, 32 mm.

Two cases of severe dehydration in psychotic, maniacal and excessively hyperactive patients in whom it was difficult to restore and maintain an adequate fluid balance (Cases XIX and XX) were studied. These two had showed oliguria and evidence of dehydration on physical examination. One showed evidence of peripheral vascular collapse and at autopsy evidence of nephrosclerosis was found. It is difficult to state that nephrosclerosis was primarily responsible for the fatal outcome, but this is another excellent example of the rôle of dehydration as the factor in production of azotemia in the presence of a low reserve kidney. The second patient (Case XX) recovered.

CASE XX. A thirty-three year old male negro was admitted March 26, 1946, because of fever. The patient had a known case of catatonic dementia praecox. Physical examination revealed a well developed, restless male. His temperature was 101.2°F.; after several hours it rose to 106.4°F. Respirations were not labored. A marked tachycardia was present, blood pressure was 110/70 and the patient perspired profusely. There was a lenticular opacity of the left eye; the fundus of the right eye was normal. The tongue and mucous membranes were dry. Examination of the chest, lungs and heart revealed no abnormalities. The abdomen was soft and there was tenderness in the left lower quadrant. After twenty-four hours the temperature had dropped to 98°F. and then rose to 102°F. on the third day, followed by a return to normal during the next four days. Three thousand cc. of parenteral fluids were given in the form of glucose and saline on the third day. The patient remained restless and hyperactive. On the sixth day a lumbar puncture was performed which revealed normal dynamics and normal spinal fluid constituents. The blood pressure remained at 110/70; heart and lung x-rays were normal. The patient became less hyperactive and was discharged after twenty-eight days in the hospital. Laboratory work revealed the following: Urinalysis: specific gravity, 1.006 to 1.010; albumin and sugar, negative; red blood cells, 0; white blood cells, 0; casts 0. Blood count: white blood cells 15,200 on entrance and 6,700 on discharge; admission differential, band forms, 12 per cent;

polymorphonuclears, 64 per cent; monocytes, 7 per cent; lymphocytes, 17 per cent. Blood chemistry: entrance non-protein nitrogen, 110.8 mg. per cent (this fell after four days to 85.6 and eleven days later to 30.9); creatinine, 1.4; cholesterol, 213; blood cultures, negative; total protein in spinal fluid, 42 and 1 white blood cell/cc. The patient was discharged clinically improved.

DIAGNOSIS

Although the syndrome of extrarenal uremia is becoming more widely known than before, adequate recognition of this condition is far from satisfactory. The diagnosis is often difficult because the clinical features are bizarre and may be overshadowed by those of the causal primary disorder. To be alert for the presence of this condition is obviously the first essential. The disorder should be sought for in patients who have been vomiting excessively, who have had prolonged diarrhea or in those suffering from severe trauma or infections. Shock, whether due to trauma, surgical operations, burns or heart disease, may precede it. More recently, Barr[18] pointed out the importance of searching for this disorder in postoperative patients who are receiving routine treatment with Wangensteen suction apparatus. One may discover extrarenal uremia in severe liver damage, in Addison's disease, in diabetic coma, or any other kind of coma and in acute severe infection.

If one thinks of the possibility of extrarenal uremia, there are several laboratory measures which establish the diagnosis. The CO_2 combining power of the blood is usually elevated to the point of alkalosis. A study of the blood chlorides reveals hypochloremia in many instances. However, when dehydration resulting from diarrhea is present, the sodium chloride of the blood may be normal and acidosis, not alkalosis, may prevail. The non-protein nitrogen of the blood is always elevated and this constitutes one of the characteristic features of the disorder. Examination of the urine may be helpful in diagnosis. Generally a scanty urine of low or normal specific gravity is present even when there is dehydration; occasionally the specific gravity is above normal. The urea content of the urine is usually good and the sodium and chlorides are much diminished. With relief of dehydration by adequate fluid administration, the urine volume increases and the specific gravity becomes normal. If, on the other hand, the specific gravity remains fixed, it may be concluded that some permanent renal damage has developed in the course of extrarenal uremia.

The patient may be irrational, irritable, may be in the twilight zone of consciousness or in a deep coma. Convulsions may occur associated with muscular twitchings as observed in genuine renal uremia. All clinical evidences of dehydration are present. The blood pressure is well below normal. There is an oliguria or a complete anuria. The eyeballs are usually sunken and soft and the pulse weak and thready. The patient presents the clinical features common to the state of shock.

TREATMENT

With the diagnosis of extrarenal uremia established, the treatment is directed to restoring to normal the volume and electrolyte composition of the blood. This is accomplished by giving the correct kind of fluid, the proper amount and at the optimal rate of administration.

Three to four thousand cc. a day of a physiologic solution of sodium chloride will usually restore the electrolyte and water balance. If, instead of alkalosis and hypochloremia, acidosis is present, intravenous injections of sodium bicarbonate or sodium lactate are beneficial. In alkalosis, normal saline solution is helpful or ammonium chloride (200 cc. of a 5 per cent solution) may be given intravenously. Hypochloremia is corrected by using physiologic sodium chloride. The underlying condition which is the key factor in bringing on extrarenal uremia must be sought for and corrected.

COMMENTS

There is no unanimity of opinion concerning the exact etiology and pathogenesis of so-called extrarenal uremia although following the earlier papers on extrarenal uremia,[4–15] many and varied conditions were pointed to as causes. Alkalosis, hypochloremia, a toxic substance from the primary disorder, an excessive elaboration of non-protein nitrogen in the presence of a low reserve kidney, either alone or conjointly, have been held responsible by some.

Conditions common to almost all patients with extrarenal uremia are dehydration, azotemia and oliguria. Low blood chlorides and alkalosis are present in most cases but not in all. Hypochloremia has been said by some to be the cause of azotemia and resultant uremia but this theory has been discarded because hypochloremia is not a constant feature. Others have proposed that alkalosis is the cause but all patients with extrarenal uremia do not have alkalosis as some have acidosis. Vomiting of high intestinal obstruction may develop before alkalosis sets in so that alkalosis cannot be considered a common factor.

Some students (Zondek, Osman and Fishberg) have searched for a common basis in all of the different types of cases. Zondek[19] differentiates extrarenal uremia and extrarenal azotemia. The latter term, he says, designates only those patients with a high non-protein nitrogen in the blood and are not due to renal insufficiency but to an excessive endogenous breakdown of body protein. Good renal function in such cases is shown by the ability to secrete urine with an optimal urea concentration and by satisfactory results of urea clearance tests. On the other hand, in extrarenal uremia there is also extrarenal azotemia but in addition to this there is renal failure. Therefore, in patients with extrarenal azotemia, extrarenal uremia may subsequently develop when renal insufficiency (functional) sets in. Blum and associates[8] described a condition which they designated as hypochloremic nephrosis. They believed that the changes were due to the lack of sodium chloride in the system. This, however, is probably another manifestation of extrarenal uremia.

Fishberg[20] was the first to suggest the rôle of decreased renal blood flow in extrarenal azotemia. He observed that the primary pathogenic factor in most, if not all instances, is a decrease in blood flow through the kidneys. He points out that in the conditions which lead to extrarenal azotemia, excessive vomiting, hemorrhage, postoperative collapse, diabetic coma, Addison's disease, coronary thrombosis and others are associated with circulatory failure. He believes that the decreased volume of blood flow through the kidneys is of fundamental importance and the basis of nearly all forms of extrarenal azotemia. The shock-like picture represents a deficiency in circulation of the blood and this in turn leads to a deficiency in glomerular activity in extrarenal uremia. After the blood volume is restored to normal the extrarenal uremia corrects itself. At autopsy hardly any changes are found such as are expected in the usual forms of renal uremia.

Osman[5] believes that the most important factor is the peripheral vascular collapse and this is the chief cause of functional (extrarenal) uremia. The syndrome is explained by Jeghers and Bakst[21] on the basis of one or more of the following mechanisms: (1) fall of blood pressure; (2) low blood sodium and chlorides; (3) increased protein catabolism; (4) liver damage and (5) renal failure due to low reserve kidney.

Fresh light is shed on the modern conception of renal function by the work of Trueta et al.[17] This work, if confirmed, will have important bearing on our knowledge of renal insufficiency, azotemia and extrarenal uremia. Briefly, these investigators believe that a delicately balanced alternative circulation exists through the renal cortex and medulla, respectively. By appropriate stimulation of the kidney the blood flow destined for the renal cortex is shunted through the vasa recta into the medulla of

the kidney. Following resection of the splanchnic nerves, the blood flow through the cortex is reestablished.

Although the vascular structure of the kidney has been closely studied for many years, complete knowledge is lacking concerning the arrangements and functions of the vasa recta. It is now considered that these structures may be called into play to furnish an alternative route for the blood flowing through the kidney whereby the important cortical circulation may to a variable degree be shut down. This physiologic mechanism may explain what occurs in a variety of conditions such as crush syndrome, renal failure after abortion and lower nephron nephrosis.[22] J. Shaw Dunn and Montgomery[23] pointed out in 1941 that in some cases of acute cortical necrosis the blood by-passed the glomeruli and went directly into the medulla by a shorter route than normal. While it is too early to be sure that the mechanism described by Trueta and associates is the common factor sought for in cases of extrarenal uremia produced by a variety of diseases, it is a theory which best explains the disorder.

Previous to this demonstration by Trueta and associates, evidence has been collected which points to a hemogenic mechanism in the production of this type of clinical picture. The term renal anoxia has been coined by Maegraith.[24] According to some authors, the prophesy of anoxemia has been fulfilled. They maintain that anoxia resulting from the shunting of blood from the cortex to the medulla explains it. Whether or not this is the mechanism brought into play in trauma and serious illness resulting in extrarenal uremia is not satisfactorily answered as yet but many think favorably of it. It has not been finally determined what stimulations are necessary to bring about this shunting of blood from the greater into the lesser circulation of the kidney. Dehydration which is constantly present has been cited as one possible impulse.

At the present time this work is speculative although interesting and important; further investigations are being made to determine the rôle of these renal changes in extrarenal uremia.

SUMMARY

1. So-called extrarenal uremia is a functional disease of the kidney which is the result of one or more disorders outside the kidney. There is no unanimity of opinion concerning the exact etiology and pathogenesis of extrarenal uremia although after earlier papers on the subject varied conditions were pointed to as causes. Alkalosis, hypochloremia, a toxic substance from the primary disorder, an excessive elaboration of non-protein nitrogen in the presence of a low reserve kidney, either alone or conjointly, have been held responsible by some writers.

2. Almost any serious illness or injury may be looked upon as a cause for extrarenal uremia and yet there is no common factor accountable for it. Some of the chief clinical characteristics uniformly present are dehydration, stupor, azotemia, low blood pressure and a shock-like appearance. In other cases alkalosis and hypochloremia are present while in others acidosis and normal chloremia exist.

3. Dissatisfaction over the term extrarenal uremia arises because it fails to differentiate the azotemias due to obstructive uropathies from the nitrogen retention of metabolic origin. Interchangeable use of the terms extrarenal uremia and extrarenal azotemia is incorrect for the latter indicates mere retention of nitrogenous substances in the blood depending on factors operating in the absence of functional renal impairment while the former is a symptom complex in which azotemia is always present.

The term is a misnomer when one considers that the chief factors responsible for the uremia occur outside the kidney and yet the ensuing uremia is a result of renal insufficiency.

4. Twenty cases were presented illustrating extrarenal uremia and types of primary diseases which can be held responsible for it, and the suggestion was made that the

common factor may be found in the new experimental work done by Trueta et al.

5. Diagnosis of the syndrome is difficult since clinical features can be overshadowed by the primary disorder. Alertness for the condition is the first essential, especially in patients who vomit excessively, have prolonged diarrhea or who suffer from trauma or infections. Unlike dehydration which causes a craving for water, alkalosis and/or hypochloremia may exist without causing an urge for salt or giving any hint of its presence. The CO_2 combining power of the blood is usually elevated to the point of alkalosis. When dehydration from diarrhea is present, the sodium chloride of the blood may be normal and acidosis may prevail.

6. Treatment is directed toward restoring to normal the volume and electrolyte composition of the blood by intravenous injections of fluids and salt.

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Seminars on Protein Hydrolysates

Chemical Considerations in the Selection of Protein Hydrolysates*

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IT is the purpose of this article to indicate some of the factors which influence the value of protein hydrolysates as adjuncts in the maintenance of optimal nutrition in man. Ultimately it may be possible to describe the requirements of an ideal hydrolysate in chemical terms. However, our present state of knowledge regarding the inter-relationships of chemical constitution and the biologic utilization of proteins and their derivatives is too incomplete to make chemical criteria sufficient for the evaluation of any product. However, there are certain standards that may appropriately be set up and according to these standards there are serious faults in some products. The bases for such criteria may be physical, chemical or biologic since all of these properties are of practical importance.

The value of parenteral hydrolysate therapy has been demonstrated beyond any question. Human subjects have been maintained in nitrogen and caloric balance for many weeks by intravenous feeding alone.[1,2] The intravenous method in itself imposes stringent requirements not only on the composition of the final product but on the manner of preparation and the control of all steps in manufacture, packaging and use. The intravenous route is chosen only when other methods of feeding are impossible. At present the choice of a product under such circumstances rests on such practical but unsatisfactory factors as freedom from unpleasant or dangerous reaction, the rate of administration that can be tolerated and ease of storage and handling. It is to the credit of the manufacturers of these preparations that the first of these considerations need seldom be considered. Although progress is being made in the direction of increasing the rate at which nitrogen may be given by vein, the best products still do not permit convenient administration of the large amounts indicated in many postsurgical patients.

The situation with regard to oral protein hydrolysates is somewhat different. Here the final product need not meet the rigid requirements necessary in intravenous preparations as to sterility, non-antigenicity and mineral content. Because of the wide variation in the chemical constitution of protein hydrolysates suitable for oral use, selection of the oral hydrolysate most suitable in a given situation is a difficult matter and one which requires the consideration of many factors.

GENERAL CONSIDERATIONS

Protein hydrolysates consist of a mixture of the hydrolytic cleavage products of protein. Complete hydrolysis results in a mixture of amino acids whereas incomplete hydrolysis produces a mixture of amino acids and peptides. The peptides may be of high molecular weight (proteoses and peptones) or of low molecular weight (a few amino acids linked together). The degree of hydrolysis of a preparation is readily estimated by determining the ratio of amino nitrogen to total nitrogen. Owing to the presence of non-amino nitrogen in some

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amino acids and derivatives, this ratio never reaches 1.0 even with complete hydrolysis but may rise to 0.8. The larger protein fragments may exhibit antigenic properties; hence more complete hydrolysis insures the absence of this undesirable feature and parenteral products usually consist of a mixture of molecules of low molecular weight.

The nutritive value of a hydrolysate depends to a large extent on the parent protein. One of the chief factors determining the biologic availability and usefulness of any protein is the pattern of amino acids of which it consists. From the work of Rose and others[3] it is generally recognized that there are about ten amino acids which the human body is unable to synthesize at a rate sufficient to satisfy normal demands. Hence, these amino acids must be taken into the body preformed in amounts sufficient to satisfy the needs of the body. The exact levels at which these "essential" amino acids must be present in the diet are not known. It has been demonstrated that a deficiency of any one of these will lead to poor utilization of the rest and it is probable that the need for each may vary from time to time depending on the particular proteins which need to be synthesized or replaced. An example of the latter point is to be found in the marked differences in the requirements of the growing versus the adult rat.

The remaining twelve amino acids are to be regarded as essential also, but these may be synthesized according to need from nitrogen of a non-specific nature provided there is a source of carbon residues over and above those which must be oxidized.

From these considerations, then, a hydrolysate which is to provide a large part of the nitrogen intake must supply: (1) Adequate amounts of the ten essential amino acids. (2) An adequate supply of total nitrogen in the form of essential or other amino acids. (3) In addition, there must be available material for oxidation, and the vitamins and minerals necessary for proper utilization of the administered nitrogen.

Commercial hydrolysates are derived from a number of protein sources. Since the biologic quality of the product closely reflects that of the protein from which it is derived, selection of starting material must be made with care. Persons on an ordinary mixed diet run little likelihood of developing an amino acid deficiency since the proteins ingested are of widely differing compositions. However, when a single protein or hydrolysate becomes the sole source of nitrogen for even a few days, the problem of its adequacy becomes acute. This is particularly true in view of the fact that hydrolysate usually is given at times when the patient has the greatest need for optimal protein nutrition. Since our knowledge of the requirement of each amino acid is so inexact, we cannot depend upon chemical analysis for evaluation of the adequacy of a preparation. Various biologic tests may be used which have considerable value. Comparison of growth rates of young rats fed the material in question with the rates obtained on a mixed diet or standard protein of known biologic value is one such test. This test suffers from the fault that (1) although the nutritional requirements of the rat resemble in many respects those of man, there may be important differences;[4] (2) the growth requirements may be very different from those in various kinds of depletion and injury.

Animals depleted of protein stores may be prepared by simple starvation or by more acute technics such as plasmapheresis. The rates of repletion in such animals give valuable information on the relative efficacy of proteins and hydrolysates. Here again may be raised the objection that animal experiments may not provide an adequate basis for the evaluation of expected performance in man. Fortunately, however, animal testing and clinical trial on the same product indicate that animal testing is usually a reliable means of estimating the general performance in man. Ideally, of course, extensive clinical trial on standard cases would be preferable.

Proteins found suitable for complete nitrogen nutrition are usually animal in origin. For large scale production obviously availability and cost are of prime importance and those usually selected are casein, lactalbumin, muscle, blood, liver and yeast protein. Sometimes mixtures of these are used to insure a well balanced product.

Hydrolysis is usually effected by means of acid or by use of proteolytic enzymes. Acid hydrolysis is readily controlled in producing up to essentially 100 per cent hydrolysis. This treatment has the disadvantage of difficulty of removal of the acid by distillation, precipitation or neutralization. Unless very mild conditions are maintained, which prevent maximum hydrolysis, one of the essential amino acids, tryptophane, is completely destroyed and this necessitates fortification of the final product with some other source of this material. Enzymatic hydrolysis is accomplished by incubating the parent protein with a source of proteolytic enzymes such as minced pancreas. The resulting product is an incomplete hydrolysate in which all amino acids remain intact and which contains no added chemicals. Complete hydrolysis is not feasible by such means and the possible presence of large polypeptides must be guarded against. A similar procedure is used with yeast preparations in which the yeast enzymes are allowed to act on the protein. Alkaline hydrolysis is never used since destruction and racemization of amino acids inevitably results.

COMMENTS

Parenteral hydrolysates represent a great contribution to the armamentarium of protein therapy. In cases in which other routes of administration are useless only human blood preparations compete with hydrolysates as sources of nitrogen. Human serum albumin, although stable and effective, is prohibitively expensive. Lyophilized plasma and whole blood are usually reserved for conditions such as shock in which protein deficiency is confined to the circulatory system and prompt repletion is essential. Here again cost and availability limit the usefulness of these natural materials for use in patients exhibiting extensive depletion and requiring prolonged high protein therapy.

As indicated before parenteral hydrolysates suffer from limitations as to rate and convenience of administration. Several studies have indicated that nitrogen balance can readily be maintained but that positive balance can be attained only with difficulty. However, recently an excellent clinical study by Hoffman and associates,[5] in which caloric and vitamin content of the diets were controlled, indicates the undoubted efficacy of an intravenously administered casein hydrolysate in attaining markedly positive nitrogen balance in depleted patients with moderately high total nitrogen intake. As much as 13 Gm. of nitrogen per day were retained on a total intake of 26 Gm. per day. Although the authors conclude that the hydrolysate was well utilized, they indicate that an even higher efficiency is obtained upon oral administration. It should be emphasized that such results can be expected only if the other nutritional factors are provided for simultaneously.[6]

In view of the rapid progress being made in the improvement of parenteral preparations there is every indication that safe, concentrated and effective products will soon be available at moderate cost. At the present time selection of a product must be made on the following points aside from the usual consideration in selecting parenteral products: (1) derived from protein of high biologic value with all amino acids conserved in the same pattern as in the protein; (2) non-antigenic (perhaps best guaranteed by high degree of hydrolysis); (3) low concentration of dicarboxylic amino acids (nausea provoking); (4) high rate of infusion; (5) stability (freedom from precipitate on standing).

In selection of an oral hydrolysate other factors must be considered: If the hydrolysate is to be used simply as a minor supplement to an already adequate diet, then the only basis for selection need be

that the biologic value be high and that it be acceptable to the patient. If the product is to form the major part of the nitrogen intake, then care must be taken that in addition to biologic adequacy the preparation must not contain elements which may be harmful in the large quantities likely to be ingested. An example of this is to be found in sodium chloride. Salt is one of the most effective agents in modifying the inherent objectionable taste of hydrolyzed protein. Its presence aids palatability of dilute solutions in amounts as high as 20 per cent. Such a preparation would contain 40 Gm. of sodium chloride if given in a quantity sufficient to provide 24 Gm. of nitrogen. In many postsurgical patients this amount of salt would almost inevitably lead to serious complications of water and salt balance. Care must be taken as with parenteral hydrolysates to include the factors necessary for proper utilization of the nitrogen. Adequate supplementation with vitamins, the minerals necessary for incorporation of nitrogen into protoplasm and adequate caloric coverage by carbohydrate and fat are all necessary.

Since normally ingested nitrogen is chiefly unmodified protein, the question arises as to what justification there is for using oral hydrolysates at all. Most available evidence indicates that any whole protein is at least as well utilized as any modified product from that protein. The advantages to be gained by hydrolyzing proteins may be summarized as follows: (1) They are less bulky and hence have a lower satiety index than natural protein sources. (2) They provide an excellent standard source of nitrogen for the study of many problems relating to protein nutrition. (3) They are usually completely soluble and hence are easy to incorporate into liquid and soft foods. (4) They appear to have some actions not related to their nutritive value which are desirable. As an example Co Tui reports a beneficial effect in obstructed cases. (5) In some cases in which digestion may be impaired they are to be preferred to protein. The first two and to some extent the third of these advantages are shared by a number of purified whole protein preparations now available.

The disadvantages of oral hydrolysates may be listed as follows: (1) they are accepted poorly by many on the basis of taste; (2) large amounts of concentrated solutions provoke nausea and diarrhea; (3) they are more expensive than natural proteins.

The intelligent selection of a protein hydrolysate is impossible unless the product is labelled clearly with the information outlined in the foregoing discussion. Such labelling should include: (1) Source of protein and method of hydrolysis. (2) Total nitrogen and extent of hydrolysis with method of determination. (3) Vitamin supplement if any. (4) Sodium chloride content. (*a*) parenteral preparations; essentially salt-free except for special uses; (*b*) oral preparations; maximum of 4 Gm. sodium for 10 Gm. total nitrogen if used as sole source of nitrogen. (5) Potassium and phosphorus content of oral preparations; both should be present in amounts sufficient to cover the incorporation of one-half the injested nitrogen into protoplasm. (6) Reference to any deviation from biologic value of the protein or modification of its amino acid pattern.

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Conference on Therapy

Therapeutic Uses of Gamma Globulin

THESE are stenographic reports of conferences by the members of the Departments of Pharmacology and of Medicine of Cornell University Medical College and New York Hospital, with collaboration of other departments and institutions. The questions and discussions involve participation by members of the staff of the college and hospital, students and visitors. A selected group of these conferences is published in an annual volume, Cornell Conferences on Therapy, by the Macmillan Company.

DR. RALPH TOMPSETT: Within the past few years there have been important advances in the preparation and clinical use of a number of products obtained by fractionation of human plasma. Some of these have received fairly extensive trial. There is the serum albumin obtained from Fraction V which is used in the treatment of shock, hypoproteinemia and edema. Isohemagglutinins have been isolated from the plasma of group specific bloods and these provide potent materials for blood grouping. Another fraction containing fibrinogen (from Fraction I) has been put to use for the local control of bleeding. From the fibrinogen fraction the material known as fibrin foam has been prepared and is used for local hemostasis in operations on the central nervous system, and also the cellophane-like material known as fibrin film which is employed as a dural substitute. Fraction I has also yielded a globulin material which is presumably deficient in patients with hemophilia. It lowers the clotting time in these patients and is known as the antihemophilic globulin which may be particularly useful in patients with hemophilia who have to undergo surgery.

The product from human plasma which has been used most extensively is gamma globulin, a protein obtained chiefly from Fraction II which contains the immune bodies against infectious disease. The applications of gamma globulin form the subject of this conference. Dr. Alfred Yankauer will open the discussion.

DR. ALFRED YANKAUER: From the number of cases of measles reported to the Health Department this year (1948) we know we are approaching the peak of a moderate sized epidemic. Although not as large as the record-breaking epidemic of 1941, it will probably be the largest one since then. Gamma globulin, also called "immune serum globulin (human)," is the most useful prophylactic material available to prevent or to modify measles. This substance is to be differentiated from the one called "human immune globulin" which is the old type of human placental globulin.

Gamma globulin came into widespread use following the American Red Cross Blood Donor Program during the war and the development by E. J. Cohn at Harvard of large scale methods for fractionating plasma. Gamma globulin is obtained from Fractions II and III, chiefly from Fraction II. It can be obtained from outdated blood, even from blood as much as a year old. In fact, preparations separated from frozen plasma four years of age contained antibody titers as high as the material prepared from fresh blood. The antibodies contained in gamma globulin are concentrated about twenty-five times in the process of separation from plasma. Because the pools of adult plasma are obtained from large numbers of donors, the antibody content is quite constant from lot to lot although some interesting variations do occur. After the influenza epidemic in 1943 it was noted that the antibody titer against the influenza A virus rose in the lots of plasma obtained all over the country. It has also been shown that antibodies are present in the blood of easterners against the virus of eastern equine encephalitis but not against the western strain.

At the present time the material in use is not pure enough for intravenous injection and must be given intramuscularly. One

must make sure the material does not get into a blood vessel. It is best given with a large needle, 18 to 20 gauge. The large needle is used because the material is so viscid that it sticks in a smaller gauge needle.

Reactions to gamma globulin are conspicuous by their absence. They occur in less than 1 per cent of cases and usually consist only of mild local tenderness. A few systemic reactions consisting of mild fever for a day or two have been reported but these have been encountered in less than 0.25 per cent of the cases.

Gamma globulin has the interesting property of inhibiting the action of complement *in vitro*. This inhibition can be reversed by the addition of serum albumin to the mixture. It does not occur *in vivo*. In humans very large doses have been used with no effect on complement. This is a property which is of no practical significance at the present time but may prove to be of some significance if a preparation suitable for intravenous injection comes into use.

I would also like to point out that the cost of manufacturing gamma globulin is very high and the administrative difficulties entailed in securing a supply of it are tremendous. Its general use as a prophylactic agent presents problems of quite a different order from that of penicillin or the sulfonamides. It is very expensive and is obtained only from humans.

The principal use for this material in medicine at the present time is to prevent or to modify measles. There have been many extensive and very well controlled studies which indicate that gamma globulin is a valuable and effective agent in preventing or modifying measles. It is well to prevent measles in all very young children and also in some older children or adults under special conditions, such as in states of general debility, pulmonary tuberculosis or other diseases, or in hospitalized patients who might present a hazard to other patients. Prevention of the disease, however, also hinders the development of an immunity against further attacks. For this reason it is our aim, in older children generally, only to modify measles and not to prevent it. There is the borderline group between the ages of three and five years in which the decision whether or not to modify or prevent measles is a matter of individual judgment. In those over five one should certainly attempt to modify the disease rather than prevent it completely.

In the early studies with placental globulin and convalescent serum it was thought that an important factor determining the effect of the dose was the lapse of time after exposure. It was believed that if the agent was given soon after exposure to measles, it would prevent the disease; if given late, around the seventh or eighth day after exposure, it would modify the disease. Studies with gamma globulin, however, have shown clearly that this is not important in determining whether the disease is prevented or just modified. The deciding factor is the dose. It may be given any time before the eighth day after exposure and it will either prevent or modify the disease, depending upon the dose. A dose of 2 cc. of gamma globulin, the contents of the standard vial now available, will prevent the disease in approximately 95 per cent of exposed, susceptible household contacts under the age of one, approximately 80 per cent in the ages of one and two, 70 per cent in the ages of three and four and 60 per cent in the ages of five and six. I should emphasize that these results are not from exposures at school or other casual exposures of one sort or another. They are obtained from individuals who are susceptible to measles and who have been intimately exposed at home.

The dose of gamma globulin used for the prevention of measles is 0.2 cc. per Kg. and the dose required for the modification of measles is 0.04 to 0.05 cc. per Kg. It is convenient to remember the dosage in terms of the standard 2 cc. vial. In general, a dose of 2 cc. prevents the disease in the age group in which measles should be prevented and modifies the disease in the older group in which measles should be modified.

I would like to point out that modified measles is a disease essentially different from regular measles. The incubation period may be lengthened, the disease is milder and many of the ordinary signs of measles may be absent. The duration of immunity from gamma globulin is no longer than two or three weeks and may be less. It is very difficult to know the exact duration of immunity because multiple exposures are so common. When loss of passive immunity is indicated in a given child by the development of measles, it is often impossible to tell which exposure was the cause of the disease.

Thus far, I have discussed the use of gamma globulin as a prophylactic following exposure to measles. Before we proceed to the consideration of other uses, it should be mentioned that in the *treatment* of measles gamma globulin is of no practical importance.

Acute infectious hepatitis is another disease in which gamma globulin has proved useful. Extensive studies in the Army and a number of studies in institutions have been reported. These leave little doubt that gamma globulin is effective in preventing acute infectious hepatitis. In control groups eight to twelve times as many individuals developed acute infectious hepatitis as compared to those exposed in whom gamma globulin was used. The doses have ranged from 0.12 to 0.3 cc. per Kg. In one study in adults a standard dose of 10 cc. proved quite effective. Again, this agent has no value in the *treatment* of this disease once it has developed.

The use of gamma globulin in the prevention of acute infectious hepatitis should be differentiated from its use in attempts to prevent homologous serum hepatitis. We have no evidence that gamma globulin itself spreads homologous serum hepatitis. It has been used in an attempt to prevent this disease in some extensive Army studies involving about 6,000 individuals who had been given blood transfusions. Doses of 10 cc. had no effect in preventing the disease. It did seem to lengthen the incubation period. After larger doses, namely, 20 cc. given in two fractions, there was some indication that it might prevent the disease; but in the particular study in which this observation appeared, there were not enough cases to make it statistically significant. However, this matter is probably of no practical importance because it is not feasible to give gamma globulin to everyone who receives a transfusion.

The available preparations of gamma globulin are of no value in the prophylaxis of mumps. Moreover, even large doses of gamma globulin are of no value in the treatment or prevention of mumps orchitis. However, gamma globulin prepared from the plasma of patients convalescing from mumps has apparently been partially effective in preventing mumps orchitis. The 20 cc. dose of gamma globulin from patients convalescing from mumps, incidentally, was equivalent to about 4,000 cc. of normal adult plasma.

Gamma globulin has been shown experimentally to act in scarlet fever in the same manner as scarlet fever antitoxin or convalescent serum. Large doses have to be used. At present it is not of practical importance in the prophylaxis or treatment of this disease.

In pertussis gamma globulin from normal individuals is of no apparent value, but the gamma globulin from hyperimmune pertussis serum is useful in the treatment and prevention of whooping cough when it is used in the same way as hyperimmune serum. The material is prepared by fractionation of the plasma from previously hyperimmunized donors. It is on the market at the present time although it is still expensive.

In experimental animals human gamma globulin has some effect in the transmission of the disease but it has never been tested prophylactically in man. It is probably impossible to do so since it would have to be used in very large numbers of people and the doses would have to be repeated throughout the summer months to make sure of the effect. In one well controlled study its use

in the preparalytic stage of poliomyelitis was found to be without value.

German measles has achieved notoriety in recent days because of its apparent effect on the fetus of the pregnant woman. We have no published reports on the use of gamma globulin in German measles. We are familiar, however, with its use in a few small institutional outbreaks. From the results in these we are doubtful of its value in the prevention of German measles. The same applies to chicken pox. Here also we are familiar with a few outbreaks in which gamma globulin did not seem to be very effective in the dosage used. It has been tried in epidemic diarrhea of the newborn, both prophylactically and therapeutically, with no effect. A trial has also been made in an influenza outbreak in a children's institution. No effect in preventing or modifying the disease was noted with the dosage used. It was tried therapeutically in an outbreak of upper respiratory infection of unknown cause in a large institution but without effect. Finally, I should mention that the material has been given to premature babies without noticeable effect on the regaining of birth weight, on mortality or on any of the other factors that were measured.

In summary, gamma globulin has two important uses: first, as an agent for preventing or modifying measles; and second, for the prevention of acute infectious hepatitis in institutional outbreaks. The New York City Health Department gives the material to physicians who desire it for their patients under five years of age who are household contacts of cases of measles. The Health Department also provides it for patients above the age of five if the physician thinks there is some special reason for protecting the particular individual. In addition, it may be obtained for use in institutional outbreaks of measles and certain other special situations.

DR. TOMPSETT: There must be many questions you want to ask Dr. Yankauer. The mechanism of action of gamma globulin is of a good deal of interest. What is known about the antibody content of this material? Despite the effectiveness of gamma globulin in the cases Dr. Yankauer has mentioned, there still seems to be a little bit of black magic about why it works. The amount of antibody added to the patient's normal supply by the usual dose of gamma globulin seems to be so small. Can anyone tell us about the antibody titers? The particular disease in which gamma globulin is most helpful is the one in which it is especially difficult to measure antibodies. How much do we know about that, Dr. Yankauer?

DR. YANKAUER: There is no way of measuring the titer of measles antibodies.

DR. TOMPSETT: In connection with gamma globulin what antibodies are measured?

DR. YANKAUER: The titer of mumps antibodies has been used a great deal. There are others, including scarlet fever antitoxin, diphtheria antitoxin, streptolysin and fibrinolysin. I think the antibodies against influenza and poliomyelitis have also been measured. I can cite more specific data on mumps antibodies. The titratable antibodies against mumps virus are ten times as high in convalescent serum as in normal serum, and twenty-five times as high in gamma globulin as in adult pooled serum. Whether this measures the factor responsible for the therapeutic result when gamma globulin is injected is another question, and I do not think we know the answer. There may well be other important factors in gamma globulin which cannot be measured in the laboratory.

DR. TOMPSETT: That is also my thought. Even a large dose of gamma globulin, namely, 10 cc., which would represent the antibody content of 500 cc. of whole blood would only increase the normal person's blood antibody content by about 10 per cent on the basis of the data you cited in connection with mumps. This would amount to ten times as much or doubling of the normal person's blood antibody content if the 10 cc. of gamma globulin had been obtained from convalescent serum. We do not know what antibody titers are necessary

for protection but since such increases in antibody content are not particularly striking it appears to me that some factors other than the added supply of antibodies might play a part in therapeutic results.

DR. YANKAUER: I would agree with that.

DR. TOMPSETT: Are there other questions?

DR. WALSH MCDERMOTT: I would like to ask Dr. Yankauer about the gamma globulin obtained from the serum of persons convalescing from mumps. First, is it available in commerce and, second, is it of any value for the prevention of orchitis when given after the parotitis has become evident?

DR. YANKAUER: The material is not available in commerce. It was manufactured just for a specific study. It prevents orchitis if it is given within the first twenty-four hours after the parotitis has developed.

DR. MCDERMOTT: How much mumps convalescent serum would have to be administered to obtain the same effect?

DR. YANKAUER: The dose of gamma globulin from serum of convalescent patients was 20 cc.; and since the antibody of the serum is concentrated approximately twenty-five times in gamma globulin, the dose of the serum would be 500 cc.

In mumps as in measles the use of large doses of convalescent serum has yielded equivocal results. Some studies reported favorable results in preventing mumps orchitis and some in preventing measles. I think the answer to the problem lies in the matter of dosage. Another aspect of this may be cited.

There has been one study of measles reported in which very large doses of gamma globulin given early in the course of the measles, but before the rash, seemed to have some effect in modifying the disease. It is very difficult to evaluate this result, of course, and only the one study has been made. The possibility of such use of gamma globulin was known from the observation that large doses of convalescent serum given early after measles had developed apparently modified the course of the disease.

DR. TOMPSETT: Are there any other questions?

VISITOR: It was mentioned that modified measles is a different disease. Is the danger of post-measles encephalitis decreased in measles modified by gamma globulin?

DR. YANKAUER: I believe that no such complication has yet been reported in a case of modified measles. I do not know of any cases of encephalitis after measles that had been modified. I would like to hear about it if anyone knows of such an occurrence.

SAME VISITOR: Do you believe that gamma globulin if given early after the development of symptoms of measles would prevent encephalitis?

DR. YANKAUER: I do not think there is enough experience with the material to be able to answer that. Encephalitis is quite a rare complication although a very serious one.

DR. TOMPSETT: There is every reason for believing that non-modified measles confers immunity against that disease. However, when the disease is altered as it is in modified measles, the question arises whether the immunity is not also changed. I wonder if Dr. Stimson can throw any light on that.

DR. PHILIP STIMSON: Regarding the immunity resulting from modified measles, I think the consensus is that, if there is enough measles to give a rash, the patient will develop a protective immunity. If the modification of the measles is carried so far as to eliminate the rash, the patient does not secure full immunity.

There are two other points which I would like to bring up. One relates to the indications for modifying measles. The Board of Health states in effect: "We will supply the gamma globulin for children up to 5 years old, and for such patients over 5 as the doctor thinks need it." It is my opinion that every susceptible person, without exception, who is known to be exposed to measles should be given at least a modifying dose of some form of protective medication. The second point relates to the preparations. Among the various concerns who

supply so-called gamma globulin, there are some who mix it with placental extract. Do you know how we can distinguish these products from those which contain only gamma globulin?

DR. YANKAUER: I am sorry I cannot answer that.

DR. TOMPSETT: Dr. Stimson, you brought up one point which, while it may be of no great importance to the practicing pediatrician, is very important to those in the home with a case of measles. In statements regarding the use of gamma globulin for the prevention or modification of measles, authors use the term "exposure." They never define it. What do you consider to be an "exposure"?

DR. STIMSON: One must consider as an "exposure" any reasonably close contact, such as in the home or at school, with a child who within four days after the contact develops the rash of measles. Count back three days from the appearance of the rash in the exposing child and you have the first day in which it was possible for the patient to transmit measles.

DR. TOMPSETT: Why is gamma globulin so effective in measles and not in scarlet fever?

DR. STIMSON: There is an interesting theoretic explanation. Gamma globulin is derived from pooled blood of the general population. Ninety per cent of the adults over twenty years of age have had measles but only 10 or 12 per cent have had scarlet fever. One might, therefore, expcet the antibodies to be in much higher concentration against measles than against scarlet fever. Very large doses of gamma globulin may reduce the incidence of complications in scarlet fever somewhat, but the result is not very striking. I think that the value of the serum does not lie solely in the antibody titer. For example, 10,000 units of scarlet fever antitoxin and 100 cc. of human convalescent serum are comparable in regard to clearing up the rash and neutralizing the toxic manifestations of scarlet fever, but the 100 cc. of convalescent serum has far fewer units of antitoxin.

DR. TOMPSETT: What is your opinion of the duration of action of gamma globulin, Dr. Stimson?

DR. STIMSON: I would expect it to be protective a little longer than two weeks, perhaps up to three weeks, since it is in effect a homologous serum. The protection obtained from the heterologous horse serum cannot be counted on for as long as two weeks. I have seen diphtheria develop as early as eight days after a prophylactic dose of diphtheria antitoxin although that is quite unusual.

DR. TOMPSETT: Are there other questions?

STUDENT: What did Dr. Yankauer mean when he distinguished home contacts from school contacts in regard to the dosage schedules of gamma globulin?

DR. YANKAUER: In the studies carried out for the evaluation of gamma globulin in measles only household contacts were used. That is an important point because school or institutional contacts have a much lower attack rate. It has been shown that a susceptible individual intimately exposed to measles in the home is much more apt to contract it than one exposed only in school. Also, the spread of measles is more likely to occur in the crowded home with poor hygiene. The National Health Survey showed clearly that measles occurred at an earlier age and spread more extensively through the family in the substandard areas. It was in these families that this dosage schedule was evaluated, but I did not mean to imply that the doses mentioned were for use only on this kind of contact.

SAME STUDENT: Is it the usual practice to give gamma globulin to school contacts?

DR. YANKAUER: As I mentioned before, it is the policy of the New York City Department of Health to supply gamma globulin only for household contacts under five years of age and for institutional contacts. That would include nursery school contacts but not children in grade school. This policy is to some extent influenced by the supply. The material is difficult to obtain. The present supply was secured from the Red Cross during the war. It is quite adequate

at the present time and with current policies, but eventually it will have to be replenished. The future supply of this material will depend on the national blood bank program of the American Red Cross. The policy is based on the important fact that measles has a high mortality rate in children under five years of age. Eighty-five per cent of the deaths occur in that age group. Its use is being restricted to the most important group although the plan to modify measles in all individuals may be a sound one.

DR. STIMSON: Preparations of gamma globulin can be bought in the drug store nowadays at $2.75 or $3.00 per vial. The price has recently gone down.

DR. TOMPSETT: I telephoned a drug store today at 3 P.M. and the current retail price quoted to me was approximately $2.25 per cc.

Dr. Yankauer, you mentioned the possibility of protecting an individual against the development of infectious hepatitis. Would you give gamma globulin to other members of the family if one individual in the family developed hepatitis? My understanding of the present status of infectious hepatitis is that it is really not very infectious under ordinary living conditions although it is quite infectious in Army camps and the like. Families want to know whether they should be given gamma globulin when one member develops infectious hepatitis.

DR. YANKAUER: It is difficult to be certain of the wisest practice in such cases. As Dr. Tompsett stated, there have not been many instances resulting from the familial spread of the disease. It is certainly possible for such spread to occur.

DR. TOMPSETT: We can state, can we not, that the danger of spread within a family is not great?

DR. YANKAUER: It does not appear to be.

DR. MCDERMOTT: I would like to ask another question about measles. It was mentioned that among the patients who have received preventive or modifying doses of gamma globulin, some have febrile illness presumed to be measles but without a rash. I would like to know how frequently such illnesses are observed. I realize the difficulty in making the diagnosis of modified measles. What interests me is the possibility that adults may develop measles many times but with a rash only once. Is there evidence that measles can be so modified as to occur without a rash?

DR. YANKAUER: Yes, I would say that there is such evidence. Cases of mild illness, with fever, conjunctivitis and perhaps a slight cough but no rash occur with sufficient frequency at the proper time after exposure when gamma globulin has been given, that it seems justified to assume they represent modified measles. It seems unlikely that they are due to some other virus infection. I wonder what Dr. Stimson would say to that.

DR. STIMSON: I think it is not an unusual experience to aim for modification and produce so much modification that one is left uncertain as to whether the slight fever is due to measles or to something else.

DR. TOMPSETT: Are there any other comments?

DR. STIMSON: There is one point I would like to stress about the actual administration of gamma globulin. One has to inject it within a very short time after loading the syringe because of its tendency to stick in the syringe.

DR. TOMPSETT: There is a long period of time, let us say during eight days after exposure to measles, when one can use gamma globulin effectively. Is it the same dose whether given on the first or last day of the period?

DR. YANKAUER: In actual practice the available period does not extend from the first to the eighth day. One usually does not know that a child has been exposed to measles until the exposing child develops a rash. Ordinarily, by that time four days have passed. From the studies with gamma globulin I would say that the dose would be the same whether given at the beginning or the end of the period in which it is known to be effective.

SUMMARY

DR. GOLD: In one of our conferences on therapy held in 1941 the topic of discussion was the use of human convalescent serum against infectious diseases. The object was to confer passive immunity for prophylaxis or for treatment in infectious diseases by the administration of antibodies obtained from humans. Human convalescent serum proved to be effective in prophylaxis against measles, in the prevention and cure of scarlet fever and there was some indication that it might be of value in mumps and whooping cough. There were serious obstacles in the way of the general development of this kind of therapy. The doses were large, the cost was high and human convalescent serum was available in only limited amounts and through special sources, as in the case of the Manhattan Convalescent Serum Laboratory which was affiliated with the Department of Health of New York City.

This conference on the uses of gamma globulin is, in a sense, an extension of that subject in line with the developments which have taken place in the past few years. Dr. Edwin J. Cohn and his collaborators at Harvard Medical School devised a method for the large scale fractionation of plasma. It has been found that the protein fraction, termed "gamma globulin" in the form in which it was isolated, contains the major portion of the antibodies against infectious diseases. The solution of antibodies obtained from human plasma or serum has now become an article of commerce and is readily available at fairly reasonable cost. It is provided by several manufacturers in 2 cc. vials under the name of "immune serum globulin (human)." It represents an approximately 16 per cent solution of gamma globulin containing the antibodies present in normal pooled plasma but in a concentration about twenty-five times that of the original plasma. In the short period of time since the isolation of this material, its utility has been explored in a number of diseases: measles, scarlet fever, mumps, whooping cough, German measles, chicken pox, infantile diarrhea, poliomyelitis, serum hepatitis, infectious hepatitis and influenza. Thus far it has proved most effective in the prophylaxis of measles and infectious hepatitis. There is some indication that it may prevent homologous serum hepatitis and that large doses may act in a manner similar to convalescent serum in the prophylaxis or treatment of scarlet fever.

The subject is still in the experimental stage. Evidence now exists indicating that some specific diseases in which gamma globulin prepared from normal pooled serum is not effective may respond to gamma globulin obtained from the plasma of patients convalescing from the disease. Thus, while the so-called "immune serum globulin (human)" has not been found effective in mumps, large doses of gamma globulin prepared from the plasma of convalescent patients have proved effective in preventing mumps orchitis, and gamma globulin prepared from the plasma of hyperimmunized donors has been found useful in the treatment and prevention of whooping cough.

The use of gamma globulin in measles was discussed in some detail. The material now available is apparently without value after the disease is established and its use is restricted to prophylaxis. When the material is given at any time between the first and eighth day after exposure, it will either prevent measles or reduce measles to a very mild disease (modified measles) depending upon the size of the dose. The view was expressed that modification of measles is desirable in most cases since this apparently allows the patient to develop full immunity while passing through a very mild form of the disease, and that the prevention of the disease is desirable in only special cases as in very young infants and under other conditions in which an active measles would give rise to special hazards either to the individual or to contacts.

The discussion also covered some of the details of administration and raised questions concerning the mode of action of gamma globulin. The current material is

suitable only for intramuscular injection and is toxic by intravenous injection. The dose for complete prevention of measles is 0.2 cc. per Kg. and only about one-fourth of that, namely, 0.05 cc. per Kg. for the modification of measles. Local and systemic reactions occur in about 1 per cent of the cases and are usually mild. An interesting point concerning the mechanism of action was raised, namely, whether the results obtained with gamma globulin are due solely to the addition of antibodies to the patient's blood. There is some indication that the amount of antibodies so added may be too small to account for the protective effects and that some factor other than added antibodies may be, at least in part, responsible for the therapeutic results.

Clinico-pathologic Conference

Acute, Severe Chest Pain with Fatal Termination*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D. and David E. Smith, Jr., M.D., of weekly clinicopathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, G. M., (B. H. History No. 62249), was a forty-six year old white, married, packing house worker who entered the Barnes Hospital for the first time in 1937 following an automobile accident in which he suffered abrasions of the scalp and right shoulder and a fracture of the left knee. At that time his blood pressure was 145/90 and there was suggestive expiratory wheezing over both lung fields but physical examination, except for the traumatic injuries noted, was otherwise negative. The laboratory data, likewise, were all within normal limits. His hospital course was entirely uneventful.

He sought admission for the second time on May 30, 1947, complaining of pain in the chest. The family history was irrelevant. He stated that in his childhood he had "bronchitis" and at the age of thirty had undergone repair of a right inguinal hernia. His general health had apparently been excellent and he was able to perform rather strenuous work in the packing house in which he was employed. He denied any history of previous chest pain. The systemic review was unrevealing. Of interest, however, was the fact that the patient had drunk and smoked excessively for many years.

There was some indication that for approximately one year the patient had noted slight shortness of breath on infrequent occasions when excited, and he had noted transient swelling of the ankles for about the same period. In general he had felt quite well until the night before entry when he complained of a feeling of "severe tightness" over the left chest which did not radiate. He took very little food at suppertime but shortly thereafter vomited some yellowish material. The sensation of pressure in the chest persisted all night and shortly after its onset the patient stated that he became short of breath. The next morning the chest pain gradually became worse and a short while before the patient presented himself in the emergency room of the Barnes Hospital the pain became crushing in character; he found it most difficult to breathe and began to perspire profusely.

At the time of entry the temperature was 36.4°c., pulse 100, respirations 34 and blood pressure 90/70. The patient was an obese white male who appeared acutely and critically ill. Although he had been given morphine immediately on entry, his pain persisted and he answered questions with difficulty. The respirations were rapid and shallow. The skin was flushed and the patient perspired profusely. Slight cyanosis of the lips and fingernails was noted. Examination of the eyegrounds was negative. The upper respiratory tract was entirely normal. The trachea was in the midline. Examination of the lungs revealed resonance to percussion, but coarse ronchi and moist bubbling râles were heard throughout the right lung field and over the left lung to a lesser extent. The heart was somewhat enlarged, the left border dullness extending 10 cm. to the left of the

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mid-sternal line in the fifth interspace. There was no right-sided enlargement. The rhythm was regular except for an occasional premature ventricular contraction. The sounds were described as being "fair to poor" in quality and at the apex a gallop rhythm was heard intermittently. There were no murmurs. The right radial pulse was somewhat faint; the left was of better quality. The peripheral vessels were moderately sclerotic. Normal pulsations were felt in the arteries of the lower extremities. The abdomen was obese and slightly distended but no tenderness or masses were elicited. The herniorraphy scar was well healed. There was 2+ pitting edema over both lower extremities. The fingers were not clubbed. Neurologic examination was within normal limits.

The laboratory findings were as follows: Blood count: red cells, 5,100,000; hemoglobin, 13.5 Gm.; white cells, 18,000; differential count: stab forms, 7 per cent; segmented forms, 80 per cent; lymphocytes, 9 per cent; monocytes, 4 per cent. Urinalysis: albumin, 3+; sugar, negative; sediment, 20 to 30 white cells per high power field with occasional red cells. The stool examination was guaiac negative. Blood Kahn test: negative. Blood chemistry: sugar, 163 mg. per cent; non-protein nitrogen, 27 mg. per cent; total protein, 5.6 Gm. per cent; albumin, 3.7 Gm. per cent; globulin, 1.9 Gm. per cent. Corrected sedimentation rate (Rourke-Ernstene): 0.3 mm. per minute. Electrocardiogram: high peaks in the T waves in leads I and II; no other abnormalities were seen.

As noted the patient had been given 15 mg. of morphine on his admission to the emergency room from which he was sent immediately to the ward and placed in a cardiac bed. Oxygen was administered by a positive pressure mask and rotating tourniquets were applied. The patient was given 0.25 Gm. of aminophylline intravenously. The blood pressure rose gradually to 100/80 during the first hour and several hours later it was recorded as 120/90. After a second injection of morphine the patient rested quietly although he continued to perspire profusely; his skin remained cool. At 9 P.M., approximately ten hours after entry, the patient coughed up about 1 ounce of material containing two large blood clots, one apparently old and one fresh. At that time examination of the chest revealed diminished breath sounds and ronchi over the left lower lung field. For the next few hours the patient continued to cough up bright red blood in small quantities. There was no calf tenderness and Homans' sign was negative bilaterally. The calf measurements were equal. The patient spent a fairly comfortable night and the next morning complained of no pain but shortness of breath was still apparent, the respirations being 30 per minute. Examination of the lungs revealed ronchi bilaterally and slightly diminished breath sounds at the left base. The heart sounds were of fair quality. The pulse was thready at a rate of 90 and the blood pressure had again fallen to 90/60. Two + pitting pretibial edema was still present. Reexamination of the optic fundi again showed no significant changes.

Another electrocardiogram was obtained. There was a diminution in the height of the T waves in leads I and II. Multiple precordial leads showed no changes in the S-T segment. During the course of the morning ronchi persisted throughout both lung fields. The heart sounds continued to be of moderately good quality and the rhythm remained regular. No gallop rhythm was audible. The skin had become warmer and the profuse perspiration had ceased. The patient's temperature was 37°C., and his pulse had risen to 105. The abdomen was slightly distended but no other significant findings were noted on physical examination. A repeat white blood cell count was 22,000 and the corrected sedimentation rate was 0.4 mm. per minute. The patient's condition continued as described without change until 9:30 P.M. in the evening of the second day when he suddenly developed pulmonary edema and, despite all emergency measures, died shortly thereafter.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: Before we discuss this case in detail I should like to ask Dr. Massie if he would make a comment on the electrocardiograms described in the protocol.

DR. EDWARD MASSIE: Although two electrocardiograms were described in the protocol, actually three were taken. The first, which was obtained at the time of admission, was in general a perfectly normal tracing. The heart rate was slightly increased to 102 to 104 per minute. The second tracing, taken a few hours later, showed no significant change from the first. The T waves were perhaps slightly lower than those seen in the first tracing but I would not be able to attach significance to either of these two records. The third set of tracings, taken during the morning of the patient's second day—the day on which death occurred—showed perfectly normal findings in leads I, II and III. Likewise, the six chest leads revealed no significant deviations from the normal.

DR. ALEXANDER: The problem presented in this case is indeed a common one—the identity of a lesion which gave rise to chest pain. Actually we have few specific clues as far as the clinical findings are concerned. I do not believe that the physical findings on cardiac examination give us much assistance but certainly one of the diagnoses which would come to mind immediately would be coronary occlusion. Dr. Massie, would you care to comment on this possibility?

DR. MASSIE: The history as it is recorded is certainly typical of coronary thrombosis. This patient developed chest pain which came on not suddenly but rather gradually. As the pain continued the patient became progressively ill, his blood pressure fell and he developed pulmonary edema. The one atypical feature in this instance is that the patient coughed up blood. Hemoptysis is not prominent in coronary thrombosis but of course can occur with certain complications. Considering the case as a whole, myocardial infarction is certainly a very good possibility.

DR. ALEXANDER: You did not take into consideration the absence of electrocardiographic findings. In a patient who had myocardial infarction would you not have expected changes to be evident at this stage of the process? The first tracing was obtained about thirteen hours after onset of the patient's pain and the final one probably forty or forty-five hours afterward.

DR. MASSIE: I agree that usually one would expect to see some suggestive changes within twenty-four to forty-eight hours of the infarction whereas, as we have just noted, tracings obtained in this case were normal. The absence of electrocardiographic changes constitutes strong evidence against myocardial infarction, particularly in view of the fact that the episode was severe enough to cause the patient's death on the second day.

DR. ALEXANDER: In other words, if no electrocardiograms had been taken, you would be more willing to accept the diagnosis of myocardial infarction than you are in view of the normal tracings?

DR. MASSIE: Yes, I think that sums up the situation quite well.

DR. CARL V. MOORE: I would like to ask Dr. Massie if he thinks the lack of electrocardiographic changes may have been due to the fact that the infarct was in the interventricular septum? Is it not true that without esophageal leads one cannot always rule out an infarct at that particular site?

DR. MASSIE: I think your point is well taken but I would be very much surprised if one would find no evidence of an infarct in any of the chest leads. In practically all instances even small lesions in the interventricular septum will lead to some changes in the chest leads. Recently, at the meetings of the American Federation for Clinical Research in Chicago, a paper was presented in which it was pointed out that although esophageal leads may furnish additional evidence of interventricular septal infarcts that procedure nonetheless is not essential. If this patient had had a septal infarct, I should have expected to find some conduc-

tion defect or some abnormality in the apical chest lead.

DR. ALEXANDER: For about a year before entry this patient apparently had had some shortness of breath and a history of transient ankle edema. Taking these findings and adding to them râles in the chest and albuminuria, could one make a fairly good case for some form of heart disease?

DR. MASSIE: I do not believe that this patient had significant chronic myocardial or valvular lesions.

DR. W. BARRY WOOD, JR.: I should like to ask Dr. Massie how he explains the fact that this patient developed acute left heart failure if he had had neither myocardial nor valvular disease. What other explanation is there for the signs of cardiac insufficiency which this man exhibited?

DR. MASSIE: I do not believe that he necessarily had heart failure. He had a history of chronic bronchitis in the years past, and I should think that the dyspnea and ronchi could have been due to chronic pulmonary disease. I am thinking, for example, of emphysema, chronic bronchitis or even bronchial asthma. I agree that terminally there was acute heart failure as indicated by pulmonary edema, but I believe pulmonary edema resulted from an acute lesion which must have affected either the myocardium or the associated greater vessels.

DR. WOOD: You will recall that the patient had ankle edema for over a year.

DR. MASSIE: That is true but on the other hand he took rather large quantities of alcohol and perhaps had either a nutritional deficiency or hepatic dysfunction.

DR. WOOD: I was impressed, Dr. Alexander, by the diastolic blood pressure of 90 which was recorded at the time that the patient was in the hospital in 1937 after his automobile accident. It seems entirely conceivable to me that the symptoms which occurred during the year prior to his final admission may have been due to hypertensive cardiovascular disease.

DR. ALEXANDER: Dr. Schroeder, do you have any comments to make on that point?

DR. HENRY A. SCHROEDER: I think Dr. Wood's suggestion is well taken. If this patient really had a persistent diastolic pressure of 90 in 1937, it is most likely that it would have risen in the ensuing ten years. It is true, of course, that some patients maintain a diastolic pressure of 90 to 100 mm. of mercury for many years without developing serious hypertension. But ten years previously, when this patient was only thirty-seven, if his diastolic pressure had been 90, it is quite likely that it would have subsequently become higher.

DR. ALEXANDER: Do you believe this man had coronary artery disease?

DR. SCHROEDER: I do not think that he had a significant amount of coronary arteriosclerosis.

DR. ALEXANDER: What other diagnoses should be entertained?

DR. JOSEPH C. EDWARDS: The presence in the urine of albumin and white cells seemed to me to be significant and I think that the diagnosis of pyelonephritis merits consideration.

DR. ALEXANDER: Since pyelonephritis is accompanied by hypertension in about 50 per cent of cases, it may have constituted the underlying lesion which subsequently led to hypertensive cardiovascular disease. I should like to ask Dr. Sale if he believes that this man could have had a dissecting aneurysm.

DR. LLEWELLYN SALE, SR.: I think that that diagnosis certainly has to be entertained although the history is not entirely typical. It would be helpful if we had a more accurate knowledge of the patient's blood pressure in the year prior to entry.

DR. ALEXANDER: It is true that a history of hypertension is of some value in making a diagnosis of dissecting aneurysm but certainly we have seen the lesion in patients who have had no hypertension. I think that the diagnosis of dissecting aneurysm is favored by the description of the chest pain which was said to have been "crushing;" that is rather typical. One of the reasons that a better history of the patient's blood pressure prior to this episode would be

helpful is that in dissecting aneurysms the fall in blood pressure at the time of the acute episode is usually not as great in magnitude as is the case in myocardial infarction.

DR. SALE: On the other hand, the patient was apparently in shock and marked hypotension is, of course, a usual feature of shock.

DR. ALEXANDER: That is true but I have actually seen patients with dissecting aneurysms who had all the classical signs of shock except that their systolic blood pressure, even to the terminal stage, remained at levels of 140 mm. of mercury. Dr. Smith, do you have any comment? Which of these two diagnoses would you care to support?

DR. JOHN R. SMITH: I think diagnoses of myocardial infarction and dissecting aneurysm have to be entertained in parallel. I actually favor the former for it seems to me that the general features and the clinical course of this man's illness was more typical of myocardial infarction than of dissecting aneurysm. The lack of electrocardiographic change does not disturb me although such changes certainly are seen in the majority of cases. Electrocardiographic changes may, however, be delayed for days, particularly if an infarct occurs in a region of the myocardium which has been previously damaged.

DR. ALEXANDER: Either of the two lesions may give rise to intense pain. Would you comment on the pain, Dr. Smith?

DR. SMITH: There are two schools of thought on the mechanism of pain in myocardial infarction. One group believes that the pain comes from fibers in the adventitia of the coronary vessels themselves and that distention of the vessels proximal to an area of thrombosis initiates the pain. The other theory holds that ischemia of the heart muscle irritates the visceral afferent fibers from the heart. These fibers course in the cardiac nerve from the myocardium through the cardiac plexus. They travel through the sympathetic chains without synapsing to the dorsal spinal nerves. Some pass through the stellate ganglion while most others pass through the upper five dorsal roots. It is thought that in a few patients fibers pass through the cervical sympathetic chain and it is this route which is thought to account for the pain in the face which occasionally accompanies angina pectoris. In others there is a generous supply of visceral afferent nerves running to the right side, and in those people anginal pain may radiate to the right arm and right chest. Afferent fibers from the aorta, in general, have the same pathways as those from the heart.

DR. SCHROEDER: I should like to differ with Dr. Smith and support the diagnosis of dissecting aneurysm of the aorta, probably in the ascending arch. I agree with Dr. Smith, however, that the absence of electrocardiographic changes does not rule out myocardial infarction since as he stated they may certainly appear quite late in the course of that lesion.

DR. ALEXANDER: I recall from the protocol that the right pulse was somewhat fainter than the left radial pulse. Unfortunately, differential blood pressures on the two sides were apparently not taken. Does this finding substantiate the diagnosis of dissecting aneurysm, Dr. Schroeder?

DR. SCHROEDER: It might if actual measurements had shown a difference in pressure in the two arms although in perfectly normal patients the blood pressure readings may be different in the two arms. Unless one knows for certain what the situation was prior to the acute episode he cannot draw definitive conclusions. It should be stated, however, that if the difference is marked then the findings usually take on real significance.

DR. ALEXANDER: Dissecting aneurysms usually occur in the ascending aorta. If a dissecting aneurysm is to explain diminution in the right radial pulse, one must assume that the dissection involves the innominate artery since the right subclavian artery comes off of the innominate. Usually if the innominate artery is involved, the internal carotid is likewise affected, and in this patient there were no clinical findings to suggest such an occurrence.

DR. WOOD: Dr. Alexander, may we ask Dr. Robert Moore to comment on the pathologic lesion in dissecting aneurysms?

DR. ROBERT A. MOORE: Dissecting aneurysm of the aorta is most frequently associated with either simple chromatropic degeneration of the media or with idiopathic cystic medial necrosis. Actually the latter is merely an advanced stage of the former. As Dr. Alexander pointed out dissecting aneurysm usually occurs in the ascending aorta; actually almost all dissections are limited to the first 5 cm. of the aorta. It is thought that the combination of medial necrosis plus the systolic thrust of the heart are the two factors which lead to actual rupture. The line of rupture almost invariably is transverse which is the reason for the postulation that lengthening of the aorta during the systolic thrust is the immediate provoking factor. It is of interest incidentally that the rupture always occurs two-thirds of the distance from the lumen of the vessel and one-third of the distance from the outside. There is one further point which I should like to make. It is often thought that an arteriosclerotic plaque in the intima gives rise to or is responsible for dissection of the aorta. Actually there may or may not be an intimal arteriosclerotic plaque at the site, but it is thought that it is not significant in the causation of dissection.

DR. PALMER H. FUTCHER: In regard to the inequality of the radial pulses we have just consulted the patient's chart and there is a definite note by Dr. James G. Hirsch, who saw this patient, that the blood pressure at the time of his examination was equal in both arms, being 115/90. Dr. Hirsch made a further note, however, substantiating the fact that on palpation the right radial pulse did seem weaker than the left.

DR. MASSIE: I think one other diagnosis should be considered, namely, that of pulmonary infarction.

DR. ALEXANDER: That is a good suggestion. This patient had edema of his lower extremities. He had râles in the chest, chest pain and hemoptyses. Although there was no calf tenderness, Homans' sign or other local evidence of phlebothrombosis, we must consider pulmonary infarct. Dr. Goldman, do you have any comment in regard to Dr. Massie's suggestion?

DR. ALFRED GOLDMAN: I agree that pulmonary infarction should be considered; I do not believe it can be completely ruled out. I should like to point out, however, that hemoptyses may complicate dissecting aneurysm for there may be dissection along one of the bronchial vessels or the aneurysm may actually rupture into the lung.

DR. WOOD: I should like to ask Dr. Virgil Scott to comment on hemoptyses in connection with aortic aneurysms. Does the occurrence of hemoptysis mean that the aneurysm has necessarily ruptured into the bronchus, or may bleeding occur without rupture?

DR. VIRGIL C. SCOTT: No, bleeding may arise as a result of pressure of an aneurysm on the bronchus or pulmonary tissue and does not necessarily indicate rupture, at least in syphilitic aneurysm.

DR. ALEXANDER: Is not the situation rather different in syphilitic aneurysms than it is with dissecting aneurysms, in that in syphilis the aneurysm tends to be saccular?

DR. WOOD: That is a good point, Dr. Alexander, but this patient had hemoptysis for almost twenty-four hours before he died and had the dissecting aneurysm ruptured into his lung he certainly would not have lived that long.

DR. EDWARD H. REINHARD: I saw a patient recently who would be of interest to discuss in this regard. The patient had coughed up blood repeatedly for several weeks. It was thought that he probably had carcinoma of the bronchus and upon bronchoscopy blood was seen coming from the left lower lobe bronchus. The x-ray findings did not aid us in establishing a diagnosis. The patient was subjected to exploratory thoracotomy and, much to our surprise, was found to have a large aneurysm of the descending thoracic aorta. The wall of the aneurysm was intact and the patient is still alive. We assumed that the bleeding had been due to erosion of the

aneurysm into the left lower lobe. May not a similar situation have obtained here?

DR. LEO J. WADE: One other cause of hemoptysis may be mentioned. In the presence of chronic passive congestion of the lung patients may cough up blood. Certainly we see that occur in mitral stenosis for example. This patient had râles in his lungs and conceivably may have had hemoptysis as a result of pulmonary hypertension.

DR. STANLEY HAMPTON: I favor pulmonary infarction rather than dissecting aneurysm for I have been impressed by the fact that in the latter pain in the back rather than in the chest is characteristic.

DR. ALEXANDER: Dr. Smith, may one differentiate between pulmonary infarction and dissecting aneurysm or myocardial infarction on the basis of the intensity of the pain? Which would be apt to be most severe?

DR. SMITH: Either lesion may cause excrutiating pain. Probably dissecting aneurysm more consistently causes greatest pain and agony.

DR. ALEXANDER: In summary, it seems that the chief possibilities in this case are dissecting aneurysm and myocardial infarction although pulmonary infarction has received some support. I believe that the consensus of opinion favors dissecting aneurysm because it would best fit all the findings, but I think we shall have to await the pathologists' findings in order to learn the identity of the lesion.

Clinical Diagnoses: ? Dissecting aneurysm of the aorta with possible erosion into a bronchus of the lung itself, ? myocardial infarction, ? pulmonary infarction.

PATHOLOGIC DISCUSSION

DR. FRANK VELLIOS: When the sternum was removed at autopsy there were 200 cc. of bloody fluid in the right pleural cavity. The left pleural cavity was obliterated by fibrous adhesions and over the lower lobe of the left lung there was a calcified focus 7 cm. in diameter and 1 cm. in thickness. In the posterior mediastinal tissue there was a massive hemorrhage which extended laterally under the calcified plaque behind the lower portion of the left lung.

The pericardial sac contained 5 cc. of clear fluid. The heart weighed 490 Gm. and the ventricular walls were markedly thickened; that of the left ventricle measured 28 mm. In the interventricular septum there were a few small foci of firm white fibrous tissue. There was a slight degree of arteriosclerosis of the pulmonary arteries and a few small yellow plaques were present in the descending portion of the aorta. Just distal to the ostium of the left subclavian artery there was a small transverse rent in the intima of the aorta which opened into a space within the aortic wall. This space extended distally for 20 cm. and divided about half the anterior circumference of the wall of the thoracic aorta into two layers, the inner of which was approximately twice the thickness of the outer. The dissected cavity within the aortic wall communicated superiorly and proximally in the region of the rent in the intima with the tissues of the mediastinum. All these tissues and spaces were infiltrated with fluid and clotted blood.

The liver weighed 1,970 Gm. and was markedly congested as was the spleen. The kidneys weighed 180 Gm. each. The cortical surfaces were slightly granular and there was one depressed scar in the left kidney.

DR. R. A. MOORE: Although the primary lesion in this case was a dissecting aneurysm of the aorta which ruptured into the mediastinum and extended particularly into the peritruncal tissues of the left lung, there were a number of features unusual to the lesion. Knowing the nature of the anatomic findings in this case, I was in a rather embarrassing position when I was asked, during the clinical discussion, to comment on the probable site of dissecting aneurysms for I knew I would mislead the clinicians. This aneurysm originated 1 cm. beyond the ostium of the left subclavian artery; taken with some of the other anatomic findings this observation casts light on the symptomatology of the case. A

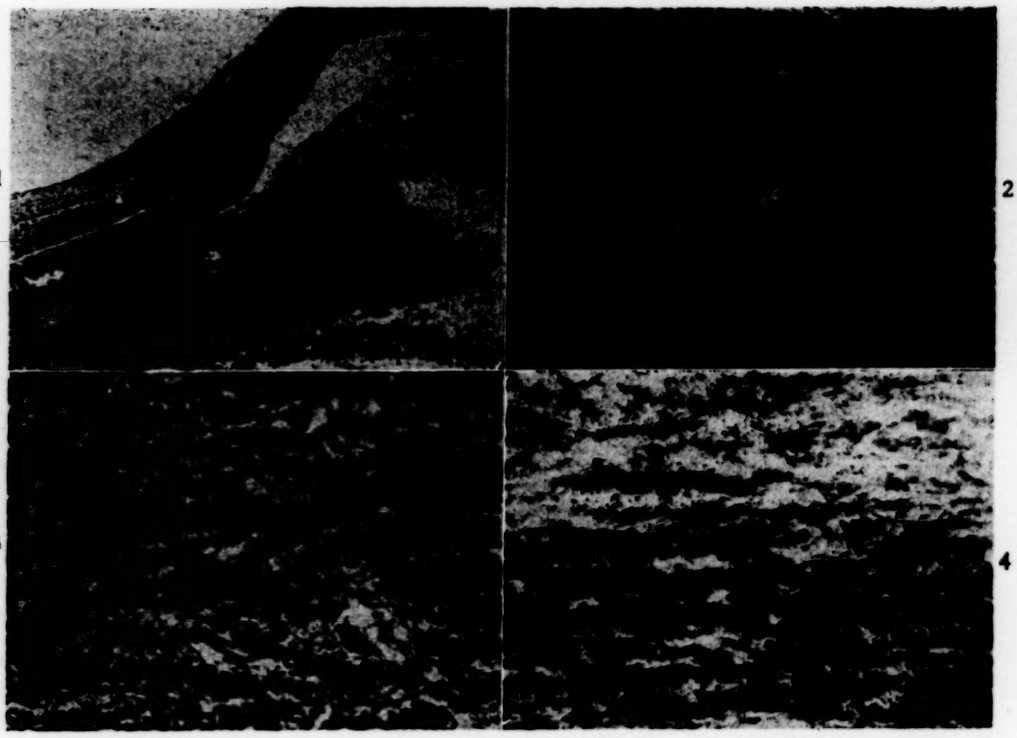

FIG. 1. Wall of the aorta at the advancing edge of the dissecting aneurysm with separation of the media by a hemorrhagic mass.
FIG. 2. Wall of the aorta with broad longitudinal band of necrotic fibers and chromatropic degeneration of adjacent viable fibers.
FIG. 3. Higher magnification of focus of chromatropic degeneration of the aortic media with small cystic foci between the elastic fibers which resemble the lesion of idiopathic cystic medial necrosis.
FIG. 4. Section stained to demonstrate fat in which the fatty degeneration which is part of chromotropic degeneration takes a dark stain.

second unusual finding was that the dissection was directed only distally and did not extend proximally toward the heart; thus, there was no *anatomic* basis for the development of the signs and symptoms of occlusion of one of the coronary arteries as occurs not infrequently in patients who have a more typical lesion. A third factor of interest was that since this dissection involved about 50 per cent of the anterior circumference of the aorta, it did not affect the intercostal vessels which arise posteriorly. The dissection also did not involve the innominate, carotid or subclavian vessels and therefore no signs or symptoms related to interruption of the circulation of any of these appeared; there was no anatomic explanation for the clinical observation that the left pulse differed in intensity from the right.

Still another feature which marks this case as an unusual one lies in the fact that in most instances the aneurysm would have ruptured into the pleural cavity and there would have been rapid exsanguination and death. As the entire left pleural cavity, however, was obliterated by fibrous adhesions the blood dissected into the mediastinum and through the pleura so that blood accumulated there and about the peritruncal tissues of the lungs. Dissection proceeded in the peribronchial tissues in much the same way as is seen when an aneurysm ruptures into the hilum of the lung. We did not demonstrate the anatomic defect where blood entered the bronchial system, but in my experience lesions such as this often rupture into one of the smaller bronchi.

In summary then, Dr. Alexander, this case of rupture of the aorta is unusual in comparison with most dissecting aneurysms. I believe the clinicians are to be commended on their attempt to make the correct

FIG. 5. Thickened arteriole in the myocardium with accompanying slight increase of interstitial fibrous tissue.

FIG. 6. Myocardium showing fragmentation and segmentation of myocardial fibers, slight increase of interstitial fibrous tissue and a focus of activated Anitschkow myocytes.

FIG. 7. Higher magnification of a focus of activated fibrous tissue with Anitschkow myocytes in the myocardium.

FIG. 8. Focus of hemorrhage and "heart failure" cells about the peribronchial tissues in the lung.

diagnosis in view of the fact that the clinical picture was altered because of the anatomic position of the rupture, the presence of pleural adhesions and other factors mentioned which forced this disease to take a somewhat different course than it usually takes.

The first photomicrograph (Fig. 1) has been selected from the border of the advancing margin of dissection near the diaphragm. One can see the aortic wall being torn apart by the fluid and clotted blood between the separated layers. The lumen of the aorta is above and the adventitia below. The dissection at this point was atypical in that it lay approximately midway between the lumen and the adventitia; in other parts of the lesion, as was pointed out in the gross examination, the findings were more typical, the inner portion being approximately twice as thick as the outer layer.

Figure 2 is a section from the aortic wall just above the point of rupture in the region of the ostium of the left subclavian artery. There is a horizontal strip of tissue through the middle of the section which has undergone complete necrosis while the tissue on each side is viable although not normal. Such a longitudinal area of necrosis in the aorta is fairly common in this disease, but I do not think that enough emphasis has been given in the literature to the relation of this change to the cause of the dissection.

Figure 3 is a higher power view of the previous section and shows the typical lesion of chromatropic degeneration; in one or two areas a lesion suggestive of idiopathic cystic medial necrosis is seen as evidenced by several definite foci in which there is no tissue. These foci contain pale basophilic, metachromatic material which stains with thionin. This substance has accumulated between the elastic fibers and in association with it there is necrosis of the immediately adjacent tissue.

FIG. 9. Clubbing of the ends of ruptured alveolar walls in the lungs.
FIG. 10. Alveolar capillaries of the lung filled with dense, acidophilic, homogeneous precipitate of proteinaceous nature.

The next section (Fig. 4) is also from the aortic wall; the light lines represent the elastic tissue and the black masses are specifically stained for fat. This change is also one of the pathologic evidences of chromatropic degeneration—fatty degeneration of the tissues of the aortic media with accumulation of fat on the surface of the individual elastic fibers.

Now let us consider the relation of this lesion to hypertension. Dissecting aneurysm of the aorta definitely occurs more frequently in patients who have hypertension. The pathologist certainly cannot make a diagnosis of hypertension *per se*, but in this patient, whose heart weighed 490 Gm., there was no other evident cause of hypertrophy and dilatation. When that observation is considered along with the finding of microscopic changes in sections of the kidney, which include thickening of the arterioles, thickening of the parietal layer of Bowman's capsule, thickening of the basement membrane of the glomeruli and slight diffuse increase in connective tissue throughout the kidney—in other words, slight arteriolar nephrosclerosis—the probability that this patient had hypertension is above 90 per cent, and possibly above 95 per cent.

In Figure 5 an arteriole in the heart is seen which shows definite thickening. There was widespread thickening of the arterioles throughout the body, indicating that the patient had generalized arteriolar sclerosis. The myocardium exhibited the effect of coronary insufficiency as evidenced by scattered small foci of increased fibrous tissue and loss of myocardial fibers. The insufficiency, however, was not of the usual sort due to arteriosclerosis of the larger vessels; rather it was apparently the result of arteriolar sclerosis; there was actually only slight arteriosclerosis of the major coronary arteries.

Figure 6 is from the heart and illustrates two interesting changes: First, there is a focus in the left central portion of the section which represents an activation of fibrous tissue in the heart muscle; this change is indicated by the proliferation of Anitschkow myocytes and is seen under a variety of conditions. Second, fragmentation and segmentation of the myocardial fibers is present. There has been a good deal of discussion as to the significance of this latter change. Dr. Otto Saphir of Chicago maintains that fragmentation and segmentation of the myocardium indicates that two conditions were in existence shortly before death: one, coronary insufficiency of such a degree as to bring about some state of slight degeneration of the myocardium and second, a sudden dilatation of the heart within the last forty-eight hours of life.

Figure 7 is a higher magnification showing proliferation of the Anitschkow myocytes in the perivascular connective tissue with development of a nodule. Many of the so-called Aschoff bodies which have been produced experimentally in animals are nothing but small nodules of proliferation

such as these; they are to be distinguished from the true Aschoff bodies seen in rheumatic fever by the absence of fibrinoid change. No fibrinoid change is present here and this type of reaction, therefore, is non-specific.

In Figure 8 a section of the lung is seen; there is a mass of "heart failure" cells and red blood cells at one point immediately adjacent to some peribronchial tissue. Such a lesion is frequently confusing. It may cast a radiographic shadow which looks very much like miliary tuberculosis. This finding constitutes evidence that, at least in some instances, the blood which finds its way into the alveoli when failure of the heart develops may be present because of actual rupture of given capillaries or small vessels rather than as a result of generalized diapediesis of red cells. In the former instance, therefore, a mass of blood may be seen in some areas and not in others. The heart failure cells are filled with hemosiderin.

This patient did have a certain degree of emphysema, and in Figure 9 there is a beautiful demonstration of what has been described in the literature for many years as the "club-ended alveolar walls" in which local fibrosis supposedly results following rupture.

The last section (Fig. 10) is of another incidental lesion for which I had hoped we might find some explanation in the discussion of this case history. In many of the pulmonary capillaries the entire lumen was occluded by granular and homogeneous acidophilic precipitate with the appearance of plasma. I thought that this man might have had some plasma concentration although the total blood protein was only 5.6 Gm. per cent at the time a determination was made during his illness. Certainly at the time of his death when the fixative acted on whatever was inside the pulmonary capillaries it precipitated a material that had a high concentration of protein.

Pathologic Diagnoses: Chromatropic degeneration of the media of the aorta; dissecting aneurysm of the descending thoracic aorta; rupture of dissecting aneurysm into the mediastinum with hemorrhage into the mediastinal and retropleural tissues, along the peritruncal tissues of the lungs and into the lower lobe of the left lung; serosanguineous hydrothorax, right (200 cc.); arteriosclerosis of the abdominal aorta, moderate; of the thoracic aorta, pulmonary and coronary arteries, slight; arteriolar sclerosis, generalized, slight; arteriolar nephrosclerosis, slight; hypertrophy and dilatation of the heart (490 Gm).

Case Report

Visceral Neuropathy Complicating Diabetes Mellitus*

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ALTHOUGH the coexistence of neurologic findings and diabetes mellitus has been recognized for perhaps eighty years, diabetic neuropathy has become a clinical entity only recently. This has been due in large measure to diligent observation on the part of several able clinicians working in busy diabetic clinics.[1,2,9,12] Their reports have stimulated others to an increasing awareness of the condition. There are, of course, a few who question the validity of diabetic neuropathy. The question is raised as to the specific relationship of this syndrome to diabetes. Although no definite proof has been brought forth to establish such a specific relationship, this syndrome is certainly seen most commonly in diabetics.

For the sake of brevity we have used the designation, "diabetic neuropathy," throughout this report to indicate a symptom-complex occurring most frequently, but not necessarily exclusively, in diabetic patients without intending to imply anything concerning its etiology. An excellent and by far the most comprehensive review of the subject by Rundles in 1945 has served to crystallize our knowledge of diabetic neuropathy in general and of its visceral manifestations in particular.[1] He has clarified the clinical picture of neurologic signs and symptoms and has stressed the involvement of the genito-urinary and gastrointestinal systems. Although the frequency of this complication is not great in his series of 3,000 diabetics (about 4 per cent), the high degree of correlation becomes apparent when one considers the background of neglected or poorly controlled diabetes and marked weight loss.

The following case is of interest because it so strikingly represents what has now come to be recognized as classical diabetic neuropathy with involvement of the somatic and autonomic nervous systems superimposed upon a background of inadequately controlled diabetes and great weight loss. The good immediate therapeutic result in this case illustrates the fact that thorough investigation and vigorous treatment are not in vain.

CASE REPORT

M. P., a thirty-three year old, white male truck driver, presented himself on September 12, 1947, complaining of a "cold" of two weeks' duration. He had had rhinorrhea during this period and a cough productive of thick yellow sputum of three days' duration. Anorexia had been present for several weeks and there had been nausea during the previous two weeks.

The patient had been a known diabetic since 1937. There had been four episodes of diabetic coma. For the past two years he had noted protuberance of the lower abdomen but without marked distress. He had had difficulty in emptying his bladder and there was a history of nocturnal incontinence. There was very little urgency. He had had diarrhea occasionally without fecal incontinence. During the two weeks prior to entry there was severe constipation. He frequently had episodes of vertigo when changing from a recumbent to an erect position. He complained of numbness of the legs, especially in cold weather, as well as aching legs and burning of the feet much of the time. There had been fleeting needlelike sensations in the arms, legs and trunk; there had been no

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disturbance of gait. He had been impotent for some months. Dimness of vision had been present for an indefinite period. There was no history of luetic or of gonorrheal infection.

The patient had been taking 37 units of protamine zinc insulin for three months but had been partaking of an inadequate diet, frequently omitting entire meals. His weight was 30 pounds below the normal figure for his age and height.

Physical examination revealed an emaciated and extremely apathetic man. There was marked pallor and weakness. The blood pressure was 108/80, respirations were 18 and the pulse was 96. The pupils were small and reaction to light was almost imperceptible. Funduscopic examination revealed many shiny plaques, exudates and punctate hemorrhages of the retina. The cranial nerves were otherwise intact. The lower abdomen was protuberant. The urinary bladder was palpated at the level of the umbilicus. The prostate was not enlarged. Rectal sphincter tone was normal and the rectum itself was filled with hard feces. All tendon reflexes were absent. There was no disturbance of sensation or of proprioception including vibratory sense. Skeletal muscle development and tone were poor.

Catheterization yielded 1,300 cc. of residual urine. The urine contained innumberable pus cells; Aerobacter aerogenes and a non-hemolytic streptococcus were grown on culture. A lumbar puncture revealed normal spinal fluid dynamics. The Pandy, Ross-Jones, Wassermann and Lange tests were negative. There was no increase in cells. An intravenous urogram taken shortly after entry demonstrated dilatation of both renal pelves and ureters. (Fig. 1.) Roentgenographic examination of the gastrointestinal tract revealed delayed gastric emptying. The head of the meal was in the proximal colon at four hours and in the transverse colon at six hours while barium remained in the stomach. (Figs. 2A and B.) There was evidence of disordered motor function of the small intestine with scattering, segmentation and hypertonicity as well as diminution of the mucosal folds.

Significant laboratory data included: fasting blood sugar, 380 mg. per cent during the early part of the hospital stay; blood urea nitrogen, 15 mg. per cent; blood Wassermann and Kahn tests, negative; the admission blood count revealed the following: hemoglobin, 13.3 Gm.; erythrocyte count, 5,230,000; leukocyte count, 15,900; hematocrit, 43 per cent; differential

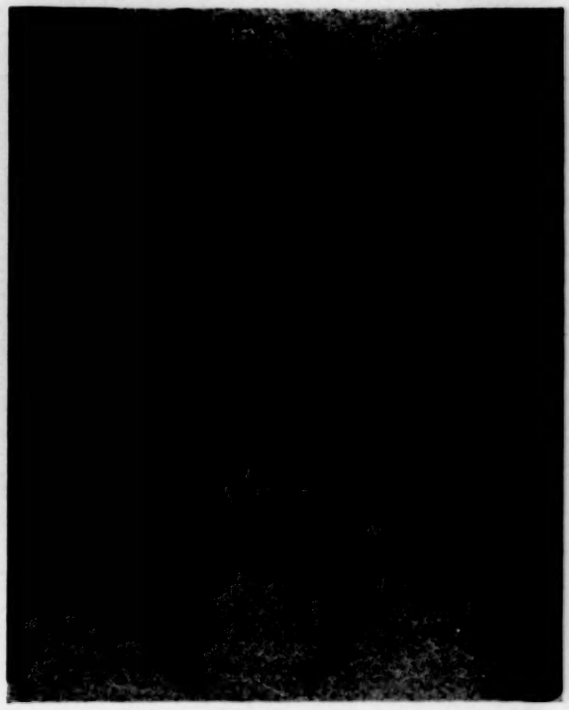

FIG. 1. Intravenous urogram showing dilatation of the ureters and kidney pelves.

count, 75 per cent neutrophiles; corrected sedimentation rate (Wintrobe), 36 mm./hour. There was no ketonuria at any time.

A urethral retention catheter was inserted at the time of admission. The urine became grossly bloody several hours afterward, although the catheter had passed easily without apparent trauma. Cystoscopic examination revealed marked hyperemia, edema and bullae formation. There was a small band of fibrous tissue in the region of the posterior urethra, not sufficiently large to produce significant obstruction.

On the fifteenth hospital day 1.9 Gm. of gray, fibrous, non-vascular tissue was resected transurethrally. There was no glandular tissue in the specimen which was reported as showing chronic urethritis. The retention catheter was removed on the third postoperative day. Prostigmine (1:2,000) was administered hypodermically every three hours from the fourth to the eighth postoperative day. When prostigmine was stopped, bladder distention without dysuria recurred. Although the bladder was distended to the level of the umbilicus, the patient stated that he had no desire to urinate. Resumption of prostigmine promptly improved bladder evacuation.

A B

FIG. 2. A and B, roentgenograms taken four and six hours after a barium meal. Note the delayed gastric evacuation and the disordered motor function of the small intestine.

In addition to the therapeutic measures already enumerated the patient received 4 Gm. of streptomycin daily over a nine-day period pre- and postoperatively. Alkalinization of the urine was achieved with the administration of 8 to 12 Gm. of sodium bicarbonate daily. Postoperatively he received sulfonamides and intramuscular penicillin for ten days. He was given a diet consisting of 350 Gm. of carbohydrate, 120 Gm. of protein and 100 Gm. of fat. Supplemental vitamins (A, B, C and D) in moderate doses were given orally. He received a maximal dose of 60 units of protamine zinc insulin and 40 units of crystalline insulin per day.

About ten days before his discharge from the hospital the patient began to display increased strength and improved appetite. Anorexia and nausea had subsided; he was taking all of the prescribed diet. At the time of discharge the insulin requirement was 26 units less than the previous maximum total daily dose. He was instructed to continue the diet as outlined. Mecholyl bromide (oral), 200 mg. three times a day, was substituted for prostigmine when he left the hospital. He was emptying his bladder well at this time. He was discharged on the twenty-seventh hospital day.

Development of bilateral phlebothrombosis of the calf muscles of the legs necessitated readmission to the hospital four days later. The response to anticoagulation therapy was good. There were no embolic phenomena. A fasting blood sugar prior to discharge was 179 mg. per cent. The patient had gained 7 pounds since his first hospital admission forty days previously.

On November 12, 1947, the patient reported that he felt very well. There was no weakness and there were no digestive symptoms. Although the urinary stream was not forceful, there was no incontinence or abdominal swelling. Dizzy spells were less severe and less frequent. He was having satisfactory sexual intercourse for the first time in a year. Aching of the legs and burning of the feet were no longer present. He still complained of dimness of vision. He had gained 11 pounds. Physical examination revealed all the neurologic findings previously described. The blood pressure in recumbency was 164/110 in the right arm and 150/108 in the left arm. The pulse rate was 100. In the erect position the pressure fell to 64/? over a five-minute period. The pulse rate rose to 120 and was barely perceptible. There was no syncope or giddiness. There was no distention of the urinary bladder. The retinal findings as described were still present. There was profuse pyuria. It was believed that the diabetes was satisfactorily controlled.

On March 13, 1948, six months after beginning treatment, the diabetes was still well controlled. Except for occasional dizzy spells, he felt quite well and was working regularly.

There had been no urinary symptoms and only an occasional white blood cell was found in the urinary sediment. His vision was somewhat improved and fewer hemorrhages were visible in the retina. His weight was 18 pounds greater than at the initial examination.

COMMENT

This case exemplifies the development of neurologic complications in a patient whose diabetes had been grossly neglected. The disease was serious enough to have resulted in diabetic coma on four occasions. Several workers, notably Jordan, have attempted to show that the occurrence of this complication bears no relation to the severity of the disease while others have stressed the importance of weight loss and uncontrolled diabetes in the majority of cases.[1-3] In Rundles' series of 125 cases with neuropathy 75 per cent had lost over 25 pounds in weight. It is of interest to note that our patient belonged to the younger age group. Jordan believes that neuropathy affects old rather than young patients; however, 25 per cent of the patients in Rundles' series were under forty years of age. Our patient was thirty-three years old when first seen, but he had had urinary retention for two years.

While there is evidence of some vesical neck obstruction in the case presented, we believed that it is the result of a neuromuscular defect leading to urine-stasis and severe cystitis of long-standing. The minor degree of obstruction, the lack of a sense of urgency in the presence of an enormously distended bladder and the favorable response to parasympathomimetic drugs would seem to confirm this opinion. The supervening mechanical defect which may be less amenable to treatment as it progresses suggests the necessity for early recognition and treatment of the neurogenic disorder.

Rudy and Muellner, in their review of eleven cases of neurogenic bladder complicating diabetes, thought that the prognosis was fair in properly treated patients. Jordan presented twelve cases of genitourinary dysfunction, seven of these with urinary retention. In the latter series urinary retention persisted indefinitely. Rundles found eighteen cases of neurogenic bladder in 125 cases of diabetic neuropathy. He noted the almost invariable association of impotence as occurred in our patient.

The relationship between diabetic retinopathy and neuropathy is undetermined. However, several studies, especially that of Folk and Soskin, suggest the close correlation between the development of retinopathy and poor diabetic control.[8]

This patient also showed evidence of orthostatic hypotension. This phenomenon was observed in eight patients of Rundles' series.

The occurrence of disordered motor function of the gastrointestinal tract in diabetic neuropathy has been recognized less frequently. Rudy has reported a case of mucosal atrophy and disordered motor function of the stomach in a diabetic with neurologic signs and symptoms and a poor nutritional background.[4] Rundles reported four cases of gastric retention and disturbed small bowel motility in his series of 125 patients with neuropathy although 61.8 per cent of the entire group had gastrointestinal symptoms, consisting of constipation, diarrhea, anorexia or nausea. However, it is well known that diabetics like other groups may have an organic disease or functional disturbances of the gastrointestinal tract unrelated to the primary disorder.

The so-called deficiency pattern is seen in a variety of diseases. It is primary, for example, in idiopathic steatorrhea but it may occur as a secondary manifestation in other disorders, such as ulcerative colitis, tuberculosis, Addison's disease and carcinoma. The roentgenographic signs include: (1) hypermotility and hypertonicity; (2) hypomotility and hypotonicity, later; (3) segmentation; (4) scattering effect; (5) delayed gastric evacuation. Pathologic examination may reveal mucosal atrophy; exaggeration of the mucosal folds may result from disturbed physiology of the

muscularis mucosa. This disordered motor function is non-specific and almost always occurs in association with malnutrition.[5] Inglefinger and Moss demonstrated the inability of the intramural plexus to liberate acetylcholine in sprue.[6] May, McCreary and Blackfan showed that injection of mecholyl improved intestinal movement and glucose absorption in celiac disease.[7] The flat oral dextrose tolerance curve in nutritional disorders may be explained by: (1) slow gastric emptying and (2) disturbed motility and mucosal changes in the small intestine. That disordered motor function of the small bowel may be part of a vicious circle in the malnourished diabetic can be readily appreciated. It is conceivable that poor control and malnutrition leading to the bowel changes just described may serve to further the state of malnutrition and impede recovery.

The mechanism of diabetic neuropathy remains obscure. Rudy has been the proponent of vitamin B deficiency.[9] There seems to be little evidence for this point of view. Most of the patients show no other evidence of vitamin deficiency; the diets of patients with neuropathy usually contain adequate thiamine; polyneuritis resulting from thiamine deficiency is a late finding.[1,2,10,11] Several workers have found thiamine ineffective in the management of this complication.[1,2] Other clinicians believe that arteriosclerosis is an important factor.[2,10,12] In spite of our ignorance of the etiology of this complication most workers agree that poor management, neglect and consequent malnutrition are important factors.

The good response to therapy in this case indicates that treatment of this complication is not hopeless. Diabetes must be well controlled. We should like to stress the importance of a diet adequate in calories and in protein content for only with such a diet can positive nitrogen balance be restored and clinical recovery be expected. Good diabetic control with only a basal diet is inadequate. The urinary tract must be investigated for a possible obstructive lesion. Slight vesical neck obstruction as the result of long-standing bladder paralysis and infection may prevent a favorable outcome; such a defect if found should be treated surgically. The use of a parasympathomimetic drug is invaluable. The choice of oral mecholyl in this case was based upon experimental observations, its prolonged action, ease of administration and low toxicity.[6,13,16] The drug has also been used in the treatment of tabes dorsalis and congenital megacolon which, incidentally, may be associated with bladder paralysis.[14,16] In our case the condition most recalcitrant to treatment was the persistent pyuria.

SUMMARY

The case of a thirty-three year old diabetic who presented the typical picture of diabetic neuropathy is reported. In addition to the more common neurologic signs and symptoms there were impaired intestinal motility, neurogenic bladder, impotence and orthostatic hypotension. Diabetic control had been poor over a period of many years. Emphasis is placed upon the early recognition and treatment of such conditions. A gratifying degree of clinical improvement was achieved in this case.

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Special Feature

American Federation for Clinical Research

ABSTRACTS OF PAPERS PRESENTED AT THE NATIONAL MEETING HELD IN ATLANTIC CITY, MAY 4, 1948.

VARIATIONS IN COLONIC LYSOZYME PRODUCTION IN VARIOUS EMOTIONAL STATES.

William J. Grace, M.D. and Paul H. Seton, A.B., New York, New York. (From the Departments of Medicine and Psychiatry of the New York Hospital and Cornell University Medical College.)

Lysozyme, a mucolytic enzyme described by Flemming in 1922, has been found by Meyer to occur in abnormally high concentrations in the stools of patients with chronic ulcerative colitis. He has produced acute ulcerative lesions in the upper gastrointestinal tract of dogs by feeding lysozyme and infers that it acts by destroying the protective mucous coating thus allowing for injury of the mucous membrane.

Our studies include the measurement of lysozyme in the stools of normal subjects, subjects with non-ulcerative diarrheas, those with ulcerative colitis in various stages of activity and the mucous secretions of a patient with ulcerative colitis who had a herniated, everted ascending colon on the surface of his abdomen. Day to day measurements were made and correlated with life situations, attitudes and feeling states.

Our findings indicate that life situations associated with emotions of hostility, resentment and guilt are accompanied by an increase in motility, vascularity and an increase in lysozyme production.

STUDY OF THE COMPARATIVE VALUE OF TETRAETHYLAMMONIUM BROMIDE AND SPINAL ANESTHESIA IN SELECTION OF HYPERTENSIVE PERSONS FOR SYMPATHECTOMY.

Louis A. Soloff, M.D. and (*by invitation*) *W. Emory Burnett, M.D.* and *C. T. Bello, M.D., Philadelphia, Pennsylvania.* (From the Temple University Hospital.)

A comparison of the results of extensive thoracolumbar sympathectomy and ganglionectomy with the preoperative responses to tetraethylammonium bromide and spinal anesthesia was made in an attempt to evaluate these two procedures as tests for the selection of hypertensive persons for sympathectomy.

There was no constant relationship of the magnitude and at times of the direction of the blood pressure changes due to the administration of tetraethylammonium bromide and that due to the production of diagnostic spinal anesthesia. In only 60 per cent of the patients was there a significant response of the blood pressure to both procedures. In some the response was greater to tetraethylammonium bromide and in others to spinal anesthesia. Significant blood pressure lowering effects due to either procedure or due to both were obtained in patients who had no postoperative blood pressure changes. Postoperative changes in blood pressure may be obtained in patients who have poor responses either to tetraethylammonium bromide or spinal anesthesia.

These procedures are not reliable in predicting the results of sympathectomy. With information available at the present time, it is advised that sympathectomy for hypertension should not be withheld on the basis of insignificant responses to tetraethylammonium bromide or spinal anesthesia.

RELATIONSHIP OF INITIAL LEVEL OF ANTIBODY TO MAGNITUDE OF ANTIBODY RESPONSE IN MAN.

Lowell A. Rantz, M.D., San Francisco, California. (From the Department of Medicine, Stanford University School of Medicine.)

Immunologists have usually described serum antibody in terms of the geometric progression of dilution systems. When this has been done, the magnitude of a response stated as tube or fold increases has varied inversely with the initial concentration of antibody.

Analysis of the data derived from the immunologic study of a large number of cases of group A hemolytic streptococcus sore throat indicates that this technic for the expression

of the results of antibody titration has obscured certain important facts. The mean magnitude of the antistreptolysin "O" response was comparable regardless of the concentration of antibody present at the onset of the infection until the decrements of serum in the system became too great to permit the measurement of response within the limits of the expected absolute increase in circulating immune substance.

It was also demonstrated that the frequency of occurrence of "significant" "two tube" increases in antibody was a function of the initial level of antistreptolysin "O." Analysis of available published data indicates that these same principles apply to the antibody response following immunization of human beings with the viruses of influenza A and B.

These observations demonstrate that antibody concentration should be expressed in terms related to the actual amounts of these substances present in the serum and that the absolute magnitude of the increase should be one of the criteria used in the evaluation of immunization procedures and in the diagnosis of infection.

INFECTIOUSNESS AND INCUBATION PERIOD OF PRIMARY ATYPICAL PNEUMONIA. *William S. Jordon, M.D., Cleveland, Ohio.* (From the Departments of Preventive Medicine and Medicine, Western Reserve University, School of Medicine.)

Clinical and epidemiologic studies have provided relatively little information as to the degree of infectiousness and the incubation period of primary atypical pneumonia. Transmission experiments in human volunteers have demonstrated that this disease can be produced by direct inoculation of respiratory tract secretions. In those volunteers who developed primary atypical pneumonia the incubation periods varied from seven to eight days when untreated inoculum was used and from eight to fourteen days, with an average of twelve days, when filtered inoculum was used. The two inocula induced atypical pneumonia in 25 per cent and 29 per cent of cases, respectively.

During the past winter seventy-two cases of primary atypical pneumonia in adults have been observed at Lakeside Hospital. Of twenty-seven patients, representing twenty-four families, twenty-five gave a history of exposure to an individual with an acute respiratory illness and two patients constituted index cases in a family outbreak of respiratory disease. In the twenty-four households acute respiratory illnesses variously diagnosed by private physicians as "severe colds," "bronchitis" or "virus pneumonia" occurred in forty-two additional persons, giving a total of sixty-nine respiratory infections in these families. Figures for total household memberships, including servants, were obtained for fifteen families and revealed that forty-nine of sixty-one individuals became ill, an attack rate of 80 per cent. Of these forty-nine patients twenty-three, or 47 per cent, were confirmed by roentgenologic and serologic studies. Two other sera were not diagnostic and we were unable to study the remaining twenty-four patients.

In twenty-one families with fifty-seven cases incubation periods from time of onset in the index cases were obtained in thirty-six instances. These periods ranged from five to nineteen days, with an average of 12.9 days.

These clinical and epidemiologic findings indicate that primary atypical pneumonia is indeed an infectious disease; it may in some instances have a high attack rate and it has an incubation period comparable with that of the experimentally transmitted disease.

TREATMENT OF PNEUMOCOCCIC MENINGITIS WITH MASSIVE DOSES OF PENICILLIN SYSTEMICALLY. *Harry F. Dowling, M.D., H. J. Hirsch, M.D.* and (*by invitation*) *L. K. Sweet, M.D., W. W. Zeller, M.D.* and *J. A. Robinson, M.D., Washington, D. C.* (From the George Washington University Medical Division, Gallinger Municipal Hospital.)

When penicillin is employed in addition to sulfonamides in the treatment of pneumococcic meningitis, the case fatality rate is reduced materially below that obtained with the use of sulfonamides alone. Among the forty patients treated in this hospital with sulfonamides alone, 93 per cent died while only 62 per cent died among sixty-six patients who received a combination of sulfonamides and penicillin systemically plus repeated intrathecal injections of penicillin. The latter method is the one which is widely used at present and consists of penicillin intrathecally in doses of 10,000 to 20,000 units of penicillin at twelve to twenty-four-hour

intervals as well as 200,000 to 500,000 units systemically during each twenty-four-hour period. Full doses of sulfadiazine or sulfamerazine are given concomitantly.

This regimen is not without many dangers however. Intrathecal injections may cause myelitis or radiculitis and intraventricular instillations may result in convulsions. Irritation of the meninges produces pleocytosis and adhesions and may result in spinal fluid block. Secondary injections are sometimes introduced when repeated lumbar punctures are done. Additional dangers are the time consumed in performing so many lumbar punctures and the annoyance to the patient which they entail.

Intrathecal instillations of penicillin continue to be employed because a number of investigators have been unable to detect penicillin in therapeutic quantities in the cerebrospinal fluid after administering it systemically. Previous studies done in our laboratory convinced us that several factors were important in obtaining and maintaining a satisfactory concentration of penicillin in the cerebrospinal fluid: (1) sufficiently large amounts of penicillin must be administered systemically; (2) the penicillin must be administered for a long enough time and (3) penicillin diffuses into the cerebrospinal fluid more freely in the presence of inflammation. When Schwemlein and his associates reported that therapeutic concentrations of penicillin could be consistently obtained in patients receiving 20,000,000 units or more during a twenty-four-hour period by continuous intravenous drip, we decided to treat all of our patients with pneumococcic meningitis with large doses of penicillin systemically. Nineteen patients have been treated in this manner up to the present time. A dose of 1,000,000 units intramuscularly every two hours was agreed upon. Spinal fluid penicillin concentrations were determined in fourteen subjects with and without meningitis. Penicillin was detectable in the spinal fluids of all of these subjects and was consistently present in every specimen obtained after the twelfth hour of treatment. Twelve of the patients except one were given sulfonamides and in addition three patients were given a single intrathecal dose of penicillin.

RATE OF MOVEMENT OF FLUID FROM VASCULAR TO EXTRAVASCULAR SPACES DURING A SYSTEMIC RISE OF VENOUS PRESSURE IN MAN. *Ellen Brown, M.D.*, and (*by invitation*) *James J. Hopper, Jr., M.D., Charles Mudrick, M.D.* and *John J. Sampson, M.D., San Francisco California.* (From the Division of Medicine of the University of California Medical School.)

Experiments were conducted to determine the effect of a systemic increase of venous pressure on movement of fluid between vascular and extravascular spaces in man. Normal subjects performed Valsalva maneuvers twice per minute for thirty minutes, resting one minute of five while blood samples were collected. Antecubital venous pressure was measured at five-second intervals by a water manometer. The overall change of venous pressure from the resting level was estimated planimetrically. Initial plasma volume was measured with T-1824. By comparison of hematocrits and protein concentrations of venous blood collected at intervals during efforts and recovery with those obtained initially, fluid movements and approximate protein concentration of the capillary filtrate could be calculated. Correction was made for the introduction of measured volumes of heparinized saline (totaling 100 to 160 cc.) required to prevent coagulation in collecting needle and manometer.

In ten experiments on six subjects overall increases of venous pressure were between 10.4 and 20.8 cm. water. Filtration occurred rapidly at first and became progressively slower. Total volumes of fluid filtered were between 184 and 680 cc., representing 4.2 to 11.0 per cent of initial blood volume. Unit rates of filtration (cc. of fluid lost per min. per Kg. body weight per cm. increase of venous pressure) were between .020 and .040 for the first nine and one-half minutes and between .010 and .024 for twenty-nine and one-half minutes of effort. While the observed unit rates for nine and one-half-minute periods were in close agreement with unit rates of filtration during local congestion of the human forearm obtained by others using different technics, the unit rates observed here for twenty-nine and one-half-minute periods were far smaller, suggesting that other factors beside rising tissue pressure were acting to conserve blood volume. In these experiments losses of fluid and protein must have occurred in trunk and extremities only because abdominal and thoracic organs were supported by pressures equivalent to the increase of venous pressure.

STUDIES ON THE MECHANISM OF REDUCTION IN RENAL FLOW IN HEART FAILURE. PRELIMINARY REPORT. *Haywood Turner, M.D.* and (*by invitation*) *David F. James, M.D.* and *Arthur J. Merrill, M.D., Atlanta, Georgia.* (From the Departments of Medicine and Physiology, Emory University School of Medicine.)

A striking reduction in renal plasma flow and filtration rate has been found in severe heart failure and is probably important in the retention of salt and water which occurs. These changes are out of proportion to the reduction in cardiac output. They appear to be due to constriction of the efferent arteriole of the kidney since the filtration rate is maintained at a relatively normal level until the renal plasma flow falls to around 200 cc. per minute. This renal vasoconstriction could be due to sympathetic stimulation or to a humoral substance. The purpose of this paper is to evaluate the rôle of the sympathetic nervous system in this phenomenon.

Since the changes in renal circulation have been shown to be related to the inadequacy of cardiac output rather than to venous pressure, a procedure which produces a reduction in cardiac output was carried out in two individuals with loss of function of the sympathetic nervous system. Tilting of a motionless normal individual to the upright position produces an average fall in cardiac output of about 20 per cent, associated with a 30 to 60 per cent fall in renal plasma flow. One sympathectomized subject and one subject with orthostatic hypotension had falls in renal plasma flow and filtration rates similar to those of normal individuals; this occurred although the blood pressure did not drop.

Spinal anesthesia was administered to three patients with heart failure and reduction in renal blood flow. Although this was carried to a level above the sympathetic nerve supply to the kidney, no increase in blood flow resulted. This could have been due to inability of the kidney to increase its flow after long-standing vasoconstriction. This seems unlikely because the depressed renal blood flow of three thyrocardiac patients returned to normal after successful treatment of the thyrotoxicosis. Seven subjects with decreased renal blood flow from congestive failure were given aminophylline with remarkable increases in cardiac output and a considerable increase in renal blood flow although the latter did not return to normal.

The above data suggest that the sympathetic nervous system is not implicated in the renal shutdown in heart failure and point to a hormonal regulation. One patient with long-standing Addison's disease who was well controlled as to blood volume and blood pressure showed a change in renal function similar to that in heart failure.

CIRCULATORY AND RENAL EFFECTS OF AMINOPHYLLINE IN CONGESTIVE HEART FAILURE. *David F. James, M.D.* and (*by invitation*) *Haywood Turner, M.D.*, and *Arthur J. Merrill, M. D., Atlanta, Georgia.* (From the Departments of Medicine and Physiology, Emory University School of Medicine).

The effects of aminophylline on patients with congestive heart failure have been studied by the simultaneous observation of the cardiac output, right atrial, pulmonary arterial and systemic arterial pressures, glomerular filtration rate, renal plasma flow and sodium excretion data. These patients were suffering from valvular heart disease and showed no evidence of primary renal disease. Aminophylline injected intravenously in 0.72 Gm. doses has been found to produce a marked increase in cardiac output, accompanied by a decrease in peripheral resistance, which is of greater degree in the pulmonary than in the systemic circulation. The fall in right atrial pressure reported by McMichael et al. to occur after aminophylline administration in such patients was also noted by us.

Increased renal plasma flow, filtration rate and an increased rejection of sodium by the tubules also took place. These renal changes are minor in degree, however, and not of an order comparable to the modification in cardiac output (which at times is nearly tripled).

The impressive diminution in pulmonary arterial pressure (in some cases as much as 20 mm. Hg mean pressure) is an expression of a lessening of the pulmonary resistance. Whether this is due to a direct action of aminophylline on the pulmonary vascular bed or is a secondary effect of improved left ventricular contraction is not known.

SOME REASONS FOR FAILURE IN USE OF DICUMAROL IN TREATMENT OF CORONARY THROMBOSIS WITH MYOCARDIAL INFARCTION. *Charles D. Marple, M.D.* (*by invitation*) and *Irving S. Wright, M.D., New York, New York.* (From the New York Hospital and the Department of Medicine, Cornell University Medical College.)

The anticoagulants, dicumarol and heparin, are used widely in the prevention and treatment of thromboembolic complications. To evaluate the use of dicumarol in the treatment of coronary thrombosis with myocardial infarction sixteen hospitals have observed one thousand patients with coronary occlusion treated similarly except that approximately one-half the patients received dicumarol in addition to conventional therapy. Dicumarol was administered usually in doses of 300 mg. the first day, 200 mg. the second day and 100 to 200 mg. on each successive day on which the prothrombin clotting time of whole plasma fell below thirty seconds as measured by the Link-Shapiro modification of the Quick one-stage technic. Heparin was administered to approximately one-sixth of the treated patients for the first few days, ordinarily in doses of 50 mg. every four hours. The following statements are based upon preliminary analysis of this material:

Failures of dicumarol therapy resulting in thromboembolic complications with or without death may occur under the following circumstances: (1) During the initiation of dicumarol therapy since significant prolongation of the prothrombin clotting time does not occur from forty-eight to seventy-two hours after administration of an adequate initial dose of dicumarol. To prevent thromboembolic complications during this period it is necessary to administer heparin concurrently and in adequate doses. (2) During the initiation of dicumarol therapy when the simultaneous administration of heparin has been discontinued arbitrarily before the prothrombin clotting time has reached an adequate level, ordinarily thirty to forty seconds. Thromboembolic complications may then occur in the interval during which neither drug is therapeutically effective. (3) When, during the course of dicumarol therapy, the prothrombin clotting time is permitted to fall below a therapeutic level. (4) When dicumarol therapy is discontinued prematurely while the hazard of thromboembolic phenomena still exists.

Hemorrhagic complications of dicumarol therapy, while infrequent and rarely severe in this series, may be anticipated in the following circumstances: (1) When the prothrombin clotting time is excessively prolonged. Bleeding is more apt to occur when the prothrombin clotting time of whole plasma is permitted to exceed sixty to seventy seconds. (2) In the presence of hepatic or renal disease when the response to dicumarol may be exaggerated and the prothrombin level may fluctuate widely. (3) In the presence of renal disease, hemorrhagic diathesis, or open lesion (e.g., peptic ulcer) when bleeding may occur at relatively normal prothrombin levels.

Ordinarily, bleeding resulting from dicumarol administration is promptly and effectively controlled by the injection of synthetic vitamin K preparations in doses of 60 to 75 mg. or by transfusions of whole blood.

There is marked variation in the response of individual patients to dicumarol and each subject must be handled as an individual problem. Some patients will tolerate excessively elevated prothrombin clotting times for a considerable period of time without bleeding. In our experience excellent therapeutic results and almost no hemorrhages have occurred when the prothrombin clotting time is maintained between thirty and forty seconds.

Dicumarol appears to reduce significantly the incidence of thromboembolic complications following coronary occlusion with myocardial infarction and does not present serious danger of hemorrhage if administered under careful supervision and adequate laboratory control.

INTRAVENOUS AORTOGRAPHY AND NEPHROGRAPHY. *H. S. Weens, M.D.* and (*by invitation*) *H. M. Olnick, M.D., D. F. James, M.D.* and *J. V. Warren, M.D., Atlanta, Georgia.* (From the Departments of Roentgenology, Medicine and Physiology, Emory University School of Medicine.)

It has been found that the human kidney parenchyma, as well as the abdominal aorta and its branches, may be opacified and visualized roentgenologically following rapid intravenous injection of 50 ml. of 70 per cent diodrast solution. The technic of injection is similar to that described by Robb and Steinberg for contrast visualization of the heart and large vessels

(angiocardiography), utilizing an antecubital vein as the site of injection. Serial roentgenograms of the abdomen in the supine position are obtained with the aid of a rapid casette changer and a self-recocking bucky diaphragm.

Thirty patients have been studied. Beginning opacification of the abdominal aorta and its branches was usually observed eight to twelve seconds following termination of the rapid intravenous injection. Four to six seconds later maximal opacification of the kidney parenchyma (nephrogram) occurred, permitting a clear differentiation of the kidney shadows from surrounding structures. In many instances, the renal cortex, medula and hilus were distinctly defined.

The results obtained compare favorably with those obtained by direct injection of the aorta. Although visualization of the aorta and its branches as described here does not attain the degree of radiologic contrast observed following aortic injection, it has the following advantages: greater ease of injection, utilization of a contrast medium safer than the sodium iodide used for direct aortography and ability to perform the procedure without special apparatus or anesthesia.

This method may be utilized not only in the study of renal circulation but also in the differential diagnosis of renal and extrarenal masses.

INTRATHECAL EPHEDRINE SULFATE ANESTHESIA IN OBSTETRICS. *W. Robert Penman, M.D., Philadelphia, Pa.* (From the Department of Obstetrics and Gynecology of the Temple University School of Medicine and Hospital.)

In the Department of Obstetrics and Gynecology ephedrine sulfate has been used to produce spinal anesthesia for delivery. When the patient is ready for delivery, she is placed on her side and the skin over the lumbar spine is prepared and sterile drapes applied. A spinal puncture is made with a spinal needle in the fourth lumbar interspace and when a free flow of spinal fluid is obtained, the anesthetic mixture is injected slowly during the intervals between uterine contractions. In this group of patients 2 ml. of a solution containing 50 mg. ephedrine sulfate and 5 per cent dextrose has been used. Following the injection, the patient is placed in the dorsal position without a pillow for a period of three to five minutes after which the table is elevated 15 degrees to aid in low fixation of the anesthetic agent.

With this technic, anesthesia adequate for delivery has been obtained in 95.4 per cent of twenty-two cases. The sensory anesthetic level rises to T-10 to T-11 and is maintained for at least sixty minutes. Motor function of the uterus and lower extremities is unaltered.

No untoward maternal complications attributable to the ephedrine sulfate injection have been observed. Likewise, fetal physiology is apparently not disturbed as evidenced by the fact that there has been no change in the fetal heart rate between the time of injection and delivery nor is there any fetal respiratory depression after delivery. At this time it appears that intraspinal ephedrine sulfate is a satisfactory anesthetic agent for spontaneous or low forceps delivery of normal patients and for the performance and repair of episiotomies.

EFFECT OF SEDATIVES ON URINARY VOLUME OF PREGNANT WOMEN. *Willis E. Brown, M.D., Otto F. Kraushaar, M.D.* and (*by invitation*) *J. T. Bradbury, Sc.D.* and *Y. K. Wang, M.D., Iowa City, Iowa.* (From the University of Iowa College of Medicine.)

In a previous communication before the Midwestern Section of this Society we have reported the effectiveness of diuretic agents in the mobilization and excretion of sodium and water. This study deals with the effect of sedatives and their antidiuretic effect.

A series of patients were given a constant intravenous infusion for five hours and hourly urine specimens were obtained for eight hours. On test days these patients were given injections of a sedative and the effect on the urinary output and chloride excretion was measured. Morphine reduced the urinary output by 50 per cent without any significant alteration in urinary chlorides. When the patient was hydrated by oral administration of fluids, morphine, demerol, codeine and amytal caused a depression in urinary volume. Paraldehyde and avertin have not been found to have an antidiuretic effect.

Additional studies were undertaken to determine the mechanism of the antidiuretic effect of morphine. By detailed studies on normal subjects and patients with diabetes insipidus it appears that this effect is not mediated by the posterior pituitary.

IMPORTANCE OF SERUM POTASSIUM IN THE SYNDROME OF HYPOPOTASSEMIA AND ITS INFLUENCE ON ELECTROCARDIOGRAMS IN PATIENTS WITH DIABETIC ACIDOSIS, *Carl S. Nadler, M.D., Samuel Bellet, M.D.,* and *Mary Lanning, B.S., Philadelphia, Pennsylvania.* (From the Philadelphia General Hospital.)

This report is based upon the changes in the electrolytes, especially potassium, which occurred before and during the treatment of forty-five patients with diabetic acidosis and the relation of these changes to their electrocardiograms.

In every patient studied the serum potassium level was found to be elevated or normal before treatment and fell to levels below normal after institution of therapy. Signs of hypopotassemia became evident during the period of three to eighteen hours after the first administration of insulin and did not necessarily parallel the severity of the acidosis. The pH of the blood showed the best correlation with the serum potassium. The carbon dioxide combining power, cation and anion concentrations, and amounts of insulin, fluids and glucose administered showed a lesser degree of correlation.

Changes in the duration of electrical systole, alterations in the amplitude of the T wave and the presence or absence of a U wave in the electrocardiogram were found to provide a reliable guide in forming an approximate estimation of the serum potassium level. Statistical correlation of these electrocardiographic changes with the electrolytic concentrations of the serum furnished strong evidence that these electrocardiographic findings and certain clinical symptoms were governed for the most part by the serum potassium level. Studies of the effects of intravenous potassium chloride add further evidence to the validity of these observations.

DISTRIBUTION OF POTASSIUM BETWEEN SERUM AND CERTAIN EXTRACELLULAR FLUIDS IN MAN. *B. P. Folk, M.D., K. L. Zierler, M.D.,* and *J. L. Lilienthal, Jr. M.D., Baltimore, Maryland.*)

In the course of studies on the effect of various concentrations of $[K^+]$ on excitable tissues it became necessary to estimate the $[K^+]$ in interstitial fluid surrounding muscle cells. Indirect estimates could be made best by determining the $[K^+]$ in serum. A review of published data revealed that the ratios of concentration in serum water and extracellular fluid water (R_{sf}) for Na^+, Cl^- and HCO_3^- indicated free diffusibility within the limits of the Gibbs-Donnan equilibrium. (R_{sf}) for $[K^+]$, however, suggested that a significant but highly variable amount of $[K^+]$ in serum was inactive. The reported (R_{sf}) for $[K^+]$ varied from 0.40 to 1.00 in the fifty-three reported studies. The average values have risen steadily since 1922 from 0.60 to 0.84 in 1934.

We have restudied the distribution of $[K^+]$ and Na^+ between serum and extracellular fluids (pleural, peritoneal and subcutaneous) in twenty-two instances in man. Analyses were made on serum (separated from cells by immediate centrifugation and recentrifugation) and on fluids by a modified Berry-Chappell-Barnes internal standard flame photometer which afforded a high degree of reproducibility and an error on recovery from biologic fluids not exceeding 2 per cent. The average (R_{sf}) for $[K^+]$ was 0.92 (range 0.82 to 1.03) and for Na^+ 0.96 (0.91 to 1.00).

This small difference might well result from leakage of $[K^+]$ from erythrocytes to serum occurring prior to separation. Theoretical calculations indicate that the loss of but 0.2 per cent of intraerythrocytic $[K^+]$ to serum will account for a drop in (R_{sf}) from 0.96 to 0.92. Indirect support for this supposition is afforded by the observation that in the dog, in which intraerythrocytic base is predominantly Na^+, the (R_{sf}) for $[K^+]$ is 0.94.

On the basis of these observations it is concluded that $[K^+]$ diffuses freely between blood and interstitial fluid. If "binding" by serum proteins exists, it would appear to be insignificant in extent.

HYALURONIDASE AND HYALURONIDASE INHIBITORS IN BODY FLUIDS IN NORMAL AND DISEASE STATES. *John K. Fulton, M.D., Stanley Marcus, Ph.D.* and *W. D. Robinson, M.D., Ann Arbor, Michigan.*

The ability of hyaluronidase to decapsulate a group c streptococcus has been standardized to permit quantitative estimation of the enzyme and to test for enzyme inhibition. The technic is capable of detecting concentrations as low as 0.01 viscosity reducing unit per cc. By this

method various body fluids in rheumatic fever, rheumatoid arthritis, pemphigus, carcinoma and in normal persons have been tested for the presence of enzyme or enzyme inhibitors. No significant alteration from the normal was found in any of these diseases except carcinomatosis when enzyme inhibition occasionally is very marked but not consistent from patient to patient. Hyaluronidase could not be demonstrated in serum of rheumatic fever, serum and joint fluid of rheumatoid arthritis nor in the serum and bullae fluid of pemphigus. Hyaluronidase is not demonstrable in sterile, fresh unextracted urine of normal or cancer patients. Salicylate, gold and PABA exert no *in vitro* inhibition of hyaluronidase in therapeutic concentrations. Urine and serum of persons taking salicylates do not contain more inhibitor substance than controls. The natural serum constituent responsible for hyaluronidase inhibition is thermolabile and appears to vary considerably in normal subjects. The mechanism of its occasional marked increase in carcinomatosis is not known.

OBSERVATIONS ON ELECTROLYTE METABOLISM IN ADDISON'S DISEASE AND GASTRIC CANCER. *Aurelia Potor, M.D., Nelson F. Young, Ph.D., F. Homburger, M.D.* and *Edward C. Reifenstein, Jr., M.D., New York, New York.* (From the Department of Clinical Investigation, The Sloan-Kettering Institute for Cancer Research Memorial Hospital Center for Cancer and Allied Diseases.)

The studies presented are the result of an inquiry into the metabolic alterations associated with neoplastic disease and the rôle of the adrenal cortex in these aberrations.

The investigation consisted of total electrolyte balance studies for a period of ten to twelve days and analysis of tissue electrolytes. In each instance sodium chloride was administered in progressively increasing amounts in constant daily increments, reaching a level of approximately 1,000 mEq. a day.

Linear representation of urinary excretion of sodium in the individuals studied permitted comparison of slopes of intake and urinary output. The resulting quotients were: normal, 0.98; Addison's disease, 0.3; gastric cancer, 0.6 to 0.75. Electrolyte distribution in tissue removed at termination of the period of large sodium chloride intake indicated a pronounced increase in sodium and chloride content and a slight decrease in potassium content of muscle from both Addison's disease and gastric cancer as compared with the electrolyte content of muscle from the normal subject.

CHANGES IN SODIUM EXCRETION IN PATIENTS WITH CIRRHOSIS OF THE LIVER FOLLOWING INTRAVENOUS ADMINISTRATION OF ALBUMIN, MERCURIAL DIURETICS AND A LOW SODIUM DIET. *William W. Faloon, M.D.* (*by invitation*), *Richard D. Eckhardt, M.D., Arnold N. Cooper, M.D.* (*by invitation*) and *Charles S. Davidson, M.D., Boston, Massachusetts.* (From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital and the Department of Medicine, Harvard Medical School.)

Repeated intravenous administration of salt-poor human albumin to twenty patients with cirrhosis of the liver led to improvement of edema and ascites in only thirteen. Failure to find a correlation between serum albumin concentration and delivery of retained fluid led to a study of other factors, especially the rôle of sodium, in fluid retention.

Diuresis with loss of ascites and edema in one patient given a 91 mEq. sodium diet promptly followed administration of albumin. Sodium excretion rose from 10 mEq. daily in the prediuresis period to 156 mEq. although the serum albumin concentration rose but slightly. Another patient similarly treated on a 123 mEq. sodium diet increased his sodium excretion from control 5 mEq. daily but to only 40 mEq. daily with little effect upon ascites and edema although albumin concentration rose to almost normal.

In spite of a serum albumin concentration maintained above 3.5 Gm. per cent by repeated injections of albumin two patients retained sodium, increased their ascites and gained weight while receiving a constant diet containing 123 mEq. of sodium daily. When the sodium intake was reduced to 21 mEq. daily, the rate of weight gain and ascites formation was markedly diminished and approximate sodium equilibrium was achieved.

Following the administration of mercurial diuretics, three patients with a dietary sodium of 21 mEq. daily showed a 6 to 10-fold increase in urinary sodium excretion and a consistent weight loss without change in serum-albumin concentration. In a patient undergoing spontaneous improvement in ascites and edema after eight months of albumin therapy excretion of sodium was found to be normal and an intake of sodium as high as 250 mEq. daily did not cause weight gain.

It is concluded that accumulation of ascites and edema in cirrhosis is primarily due to diminished ability to excrete sodium. This may be partially overcome by administration of albumin or mercurial diuretics and prevented, in part, by use of a low sodium diet.

EFFECT OF CARONAMIDE AND HEPARIN ON THE COAGULATION TIME OF HUMAN BLOOD. *Howard Sirak, M.D.* and (*by invitation*) *Curtis P. Artz, M.D., Columbus, Ohio.* (From the Department of Surgery, the Ohio State University College of Medicine.)

Papers previously written on caronamide have been concerned with its use in enhancing penicillin blood levels. Apparently, 4′ carboxyphenylonethanesulfonalide (caronamide) produces this effect by inhibiting the excretion of penicillin by competing for the renal enzyme transport mechanism. Caronamide, which has a very low index of toxicity, produces a similar effect upon para-aminobenzoic acid, diodrast and other compounds totally unrelated structurally. It was hoped that caronamide might cause a similar prolongation or enhancement of the heparin effect upon coagulation, thereby reducing the cost and facilitating the administration of heparin.

Ten patients were selected for the first part of this study. The effect of caronamide and heparin in saline was determined as follows: A control heparin tolerance test was performed on the first day. On the second day a single oral 4 Gm. dose of caronamide was given. No further caronamide was administered throughout the experiment. The heparin tolerance test was then started one-half hour later and repeated on subsequent days.

This resulted in a gradual progressive enhancement of heparin effect for the first two days, a sharp peaking on the third or fourth day and then a gradual decline to control levels by the sixth or seventh day following caronamide administration. The "twenty-minute" blood sample always demonstrated the greatest enhancement. In eight of ten cases the prolongation of the coagulation time of this sample (at the peak period) was two to ten times greater than the corresponding sampe of the pre-caronamide control period. Heparin levels performed simultaneously bore no correlation to the coagulation times.

In the second part of the study, using heparin in gelatin menstruum, caronamide demonstrated its effectiveness in reducing, approximately by one-half, the amount of heparin in gelatin menstruum needed to maintain a therapeutic elevation of the coagulation curve. This effect was achieved by using a combination of caronamide and heparin/saline injected intravenously as a priming dose, plus multiple oral doses of caronamide. The priming dose was injected. After an interval it was followed by heparin/gelatin and the first of the multiple doses of oral caronamide.

The result was a marked enhancement of the coagulation times of the heparin/gelatin curves. A quantity of heparin/gelatin produced no appreciable effect on the coagulation time; however, this same quantity, when combined with caronamide, effected a marked enhancement of the coagulation time into and beyond therapeutic levels.

EFFECT OF A PTEROYLGLUTAMIC ACID INHIBITOR IN LEUKEMIA AND RELATED DISORDERS. *Rosalie B. Neligh, M.D., Frank H. Bethell, M.D.* (*by invitation*) and *Muriel C. Meyers, M.D., Ann Arbor, Michigan.*

Fourteen patients with leukemia and related disorders were treated with a pteryolglutamic acid inhibitor (4-amino pteroylglutamic acid). The cases included three of acute or subacute myelogenous leukemia, three of early and two of advanced chronic myelogenous leukemia, two of chronic lymphocytic leukemia, two of leukemic lymphosarcoma, one of monocytic leukemia and one of multiple myeloma.

The material, which was not a pure compound, was given either orally or parenterally in daily doses ranging between 2.5 mg. and 30 mg. The most consistent finding was a decrease in the total granulocyte count which became apparent from three to fourteen days after the

start of the treatment, usually without a significant change in the differential count. Changes in erythrocyte and platelet values were variable but prolonged administration of the larger doses appeared to depress the formation of these elements. Sternal marrow aspirations revealed a progressive decrease in myeloid activity affecting chiefly, but not exclusively, the granulopoietic elements.

In some patients with myelogenous leukemia, splenomegaly decreased and symptoms of hypermetabolism subsided during therapy. On its discontinuance increased activity of the leukemia process rapidly recurred. Observations on one patient indicate that reversibility of the effect of the inhibitor by simultaneous administration of pteroylglutamic acid may be produced.

The course of the disease in the advanced or acute cases was not materially influenced by administration of 4-amino pteroylglutamic acid. Whether or not the compound will have practical value in the management of suitable cases of chronic leukemia remains to be determined. Early experiences indicate that 4-amino compound and other structural analogues of folic acid may be of importance in the study of the growth requirements of both normal and leukemic tissue.

RECENT CLINICAL STUDIES WITH PARA-AMINOBENZOIC ACID. *Chris J. D. Zarafonetis, M.D. (introduced by Sibley W. Hoobler, M.D.), Ann Arbor, Michigan.*

Para-aminobenzoic acid in the form of sodium para-amino-benzoate (NaPAB) was administered in large doses to thirteen patients with leukemia. Six patients with chronic myelogenous leukemia had a definite decline in their white cell count. Transient clinical improvement was observed in some of these patients. Upon discontinuation of the drug, the leukocyte count increased. It was impossible to evaluate the effects of NaPAB in the seven patients who had other forms of leukemia. NaPAB appeared to exert an inhibitory effect on all phases of granulocyte development. No specific alterations in differential counts were attributable to its action. Vacuolation appeared in the myeloblasts and promyelocytes during treatment.

In ten of eleven patients with lupus erythematosus there was improvement in the skin lesions following administration of NaPAB. Improvement was most marked in patients who exhibited photosensitivity and had "active" lesions associated with burning and/or itching. During treatment such lesions showed gradual fading of erythema and diminution of infiltration and edema. After NaPAB therapy was discontinued the lesions usually reappeared. In three patients the lesions again regressed upon resumption of NaPAB therapy.

Similarly, administration of NaPAB to three patients with dermatitis herpetiformis and to two patients with active dermatomyositis resulted in objective improvement.

Renal glycosuria occurred during NaPAB therapy. Dermatitis medicamentosa was encountered once.

It is emphasized that NaPAB is not a cure for these varied conditions of unknown etiology. These findings, however, along with previous observations, indicate a broad range of physiologic activity for this compound.

RAPID SLIDE TEST FOR HETEROPHILE ANTIBODIES IN INFECTIOUS MONONUCLEOSIS. *W. C. Moloney, M.D.* and (*by invitation*) *L. Malzone, M.D., Boston, Massachusetts.* (From the Clinical Research Laboratory, Holy Ghost Hospital, and the Medical Department Tufts Medical School.)

Several investigators have postulated the presence of blocking or incomplete antibody in the sera of patients with infectious mononucleosis. For the past three years studies have been carried out in a large group of individuals employing a slide technic modified after Diamond's test for Rh antibodies.

The test is carried out by mixing defibrinated or citrated sheep's blood (0.1 cc.) with serum to be tested (0.2 cc.) on a glass slide. Tests were considered positive only if 3 plus to 4 plus macroscopic clumping occurred within thirty to sixty seconds. Sera were also examined by the Paul-Bunnell test and a serum dilution of 1:112 was the lowest considered a positive reaction.

Of the 407 individuals studied very few positive tests were encountered except in infectious mononucleosis. (Table 1.) The nature of the agglutinin in the three cases of cirrhosis and the one case of myeloma was not determined. The positive slide tests found in infectious mononucleosis, with one exception, occurred only when the saline agglutinating heterophile antibody was present in a diagnostic serum dilution level. There has been little evidence thus far

in this study for the presence of incomplete or blocking antibody for sheep cells in infectious mononucleosis.

As a practical test the slide method seems to be a rapid and useful procedure in the diagnosis of infectious mononucleosis.

TABLE 1
RESULTS OF ANTIBODY STUDIES ON THE SERA OF 407 INDIVIDUALS

Diagnosis	No. Cases	Positive Slide Test	Positive Paul-Bunnell Test
Infectious mononucleosis	29	29	29
Infectious mononucleosis*	6	1	0
Infectious hepatitis	17	0	0
Cirrhosis of the liver	24	3	0
Pregnancy	95	0	0
Malignancy	30	0	0
Cord blood	23	0	0
Myeloma	2	1	0
Acute hemolytic Anemia	6	2†	0
Iso-immune anti-Rh	10	0	0
Iso-immune anti-A_1	2	0	0
Iso-immune anti-A_2	1	1	1
Iso-immune anti-B	1	0	0
Miscellaneous diseases	50	0	0
Controls	110	0	0

* These cases were clinically and hematologically typical of infectious mononucleosis.

† Tests were negative when carried out at 37°C. by the slide method.

NITROGENOUS CONSTITUENTS OF THE URINE FOLLOWING SEVERE BURNS.*

Kendall Emerson, Jr. M.D. and (*by invitation*) *Otto F. Binkley, M.D., Boston, Massachusetts.* (From the U. S. Naval Medical Research Unit No. 2.)

Two patients were studied following first and second degree burns involving 60 and 40 per cent of their body surface, respectively. The daily urinary excretion of total nitrogen, urea plus ammonia nitrogen, alpha amino nitrogen by the ninhydrin method and total amino nitrogen after hydrolysis by the nitrous acid method was measured. During the first ten days following the burns these patients excreted a daily average, respectively, of 26.88 and 13.69 Gm. of nitrogen. This included 22.65 and 12.03 Gm. urea plus ammonia nitrogen, 0.638 and 0.310 Gm. alpha amino acid nitrogen and 3.53 and 1.90 Gm. total amino nitrogen. The nitrogen excretion remained constantly elevated throughout the febrile period following the burn and showed no correlation with the nitrogen intake which was varied from 5.60 to 53.75 Gm. per day. Twenty Gm. of a synthetic mixture of the ten essential amino acids administered daily by vein for five to seven days during periods of low protein intake failed to affect the urinary nitrogen excretion except to increase the output of alpha amino nitrogen by approximately 0.25 Gm. per day, equivalent to 8 per cent of the amount administered. In spite of this both patients showed a rapid rise of plasma protein concentration during amino acid administration while they were still febrile and in negative nitrogen balance.

Total amino nitrogen in the urine remained elevated for approximately three weeks in both patients whereas urinary alpha amino nitrogen returned to normal in ten days or less. It is suggested that the increase of urinary amino nitrogen represents incomplete or abnormal protein breakdown products absorbed from the injured areas.

* The Bureau of Medicine and Surgery of the Navy does not necessarily endorse the views or opinions which are expressed in this paper.

PHOTOMICROGRAPHS OF HUMAN CARCINOMA TAKEN WITH THE POLAROID COLOR-TRANSLATION ULTRAVIOLET MICROSCOPE.*

Robert C. Mellors, M.D., New York, New York. (From the Sloan-Kettering Institute for Cancer Research, Memorial Hospital.)

Many objects not apparent in visible light are discernible in ultraviolet light because of inherent differences in ultraviolet absorption. This was recognized by Köhler who in 1904 described the first ultraviolet microscope. Indeed, the method described by Köhler and at a later date brilliantly extended by Caspersson depends upon the characteristic ultraviolet absorption of the nucleic acids which are prominent chemical constituents of chromosomes and other cell structures.

* This work was done in part under a Fellowship Grant of the American Cancer Society recommended by the Committee on Growth of the National Research Council and under contract with the Office of Naval Research, in cooperation with the Sloan-Kettering Institute.

The human eye constitutes a discriminately sensitive visual spectrophotometer. If ultraviolet absorption in the cell could be translated quantitatively in terms of visible light absorption, then the visual mechanism could be employed. At a glance the color translation method should reveal differences in ultraviolet absorption which otherwise could be shown only by time-consuming microphotometry. Such a principle was first formulated by the Russian scientist, Brumberg, in 1939. In this country the polaroid research group has worked for nearly a year on the technic of color-translation ultraviolet microscopy and on the development of better ways of examining fixed and living cells.

A preliminary study has been made of tissue sections, smears and cells in tissue culture. Photomicrographs have been taken with the polaroid design reflecting ultraviolet objectives each at three wavelengths: 260, 280 and 300 $\mu\mu$, respectively. The three black and white negatives which serve as color separation negatives for the three primary colors are then translated into full color by the polacolor process. The results may be summarized as follows: The color-translation ultraviolet photomicrographs are comparable in appearance to tissue sections stained with a polychrome dye. At the state of our present knowledge, however, the analysis of the color differences between various cytologic and histologic components in terms of chemical differences cannot be put forth.

Book Reviews

A Manual of Pharmacology. By Torald Sollmann. 7th ed., 1132 pp. Philadelphia, 1948. W. B. Saunders Company. *Price* $11.50.

The comprehensive and meticulous discussions, exhaustive documentation, and conscientious attention to recent advances which characterized previous editions extend to the seventh edition. The bibliography of this volume is very extensive despite the fact that the author has drawn mainly from the literature of the past twenty years. Drugs of recent interest, such as BAL, bacitracin, ANTU, folic acid, nitrogen mustards, antihistaminics and anticholinesterases are discussed as fully as available data permit. Reading is facilitated by a two-column format.

The vast scope of this work introduces problems in arrangement and selection which are not always solved successfully. There sometimes seems to be a lack of consistency in the order in which various aspects of the pharmacology of various drugs are considered; and occasionally it is not clear why certain topics have been assigned greater or lesser importance by relegating them to larger or smaller type. A paucity of structural formulas and illustrative charts and diagrams sometimes deprives the presentations of incisiveness.

In the opinion of the reviewer this book constitutes an invaluable reference manual for persons actively working in pharmacology or allied fields. The deficiencies in presentation of subject matter somewhat impair its usefulness as a teaching textbook.

I.A.C.

The Engrammes of Psychiatry. By J. M. Nielsen, M.D. and George N. Thompson, M.D. Pp. 509. Springfield, Ill., 1947. Charles C. Thomas. *Price* $6.75.

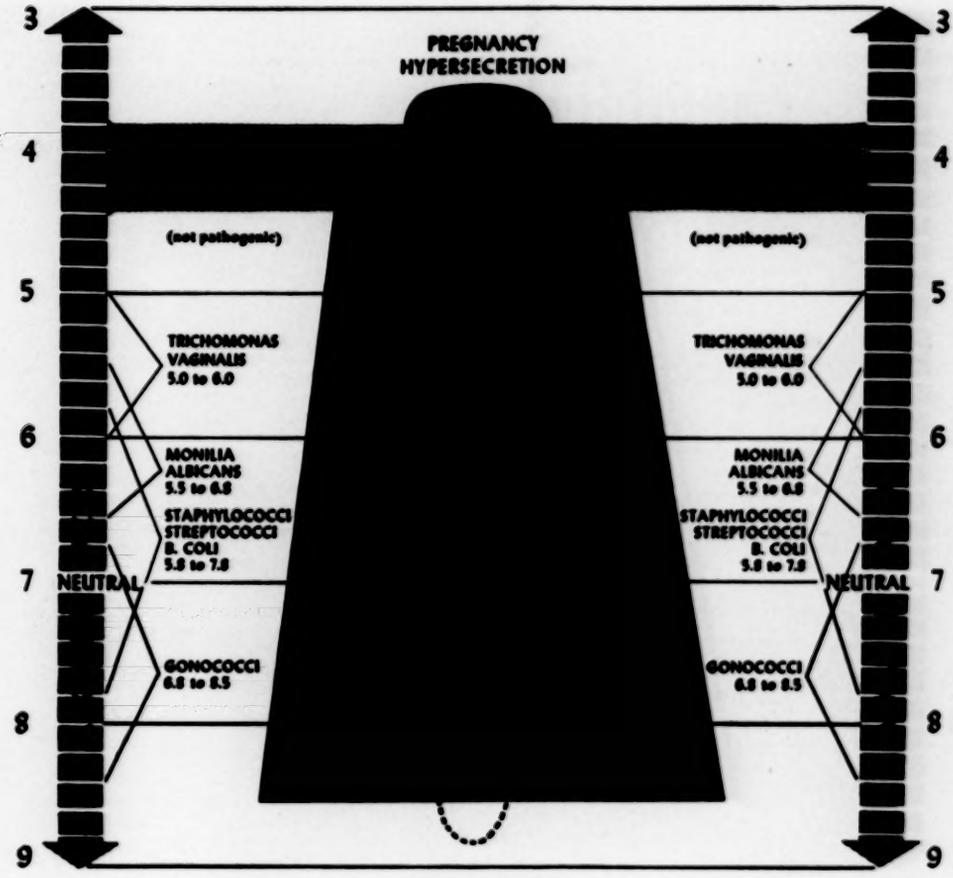
The authors have prescribed a book which is an attempt to put psychiatry in the same anatomic and localizing plane as neurology. They try to localize such mental functions as conation, consciousness, awareness, etc., in specific areas of the brain. The evidence given is certainly inconclusive and not scientific.

In the Psychoneuroses, the authors suggest the probability of an "underlying psychopathological mechanism" and the ability to find this depends upon the skill of the examining person. Although the mechanisms may be Freudian, the authors themselves do not seem convinced and hence certainly make no convincing impression upon the reader.

Psychopathic personality, schizophrenia and manic depressive psychoses originate in organic cerebral disturbances. The first may be frontal lobe and the latter two diencephalic. The authors do admit, however, to a large constitutional factor in manic depressive psychosis and schizophrenia.

The book would tend to lull students and other readers into a false sense of security. It gives the impression that psychiatry is far more advanced than it actually is.

S.D.



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RESEARCH IN THE SERVICE OF MEDICINE

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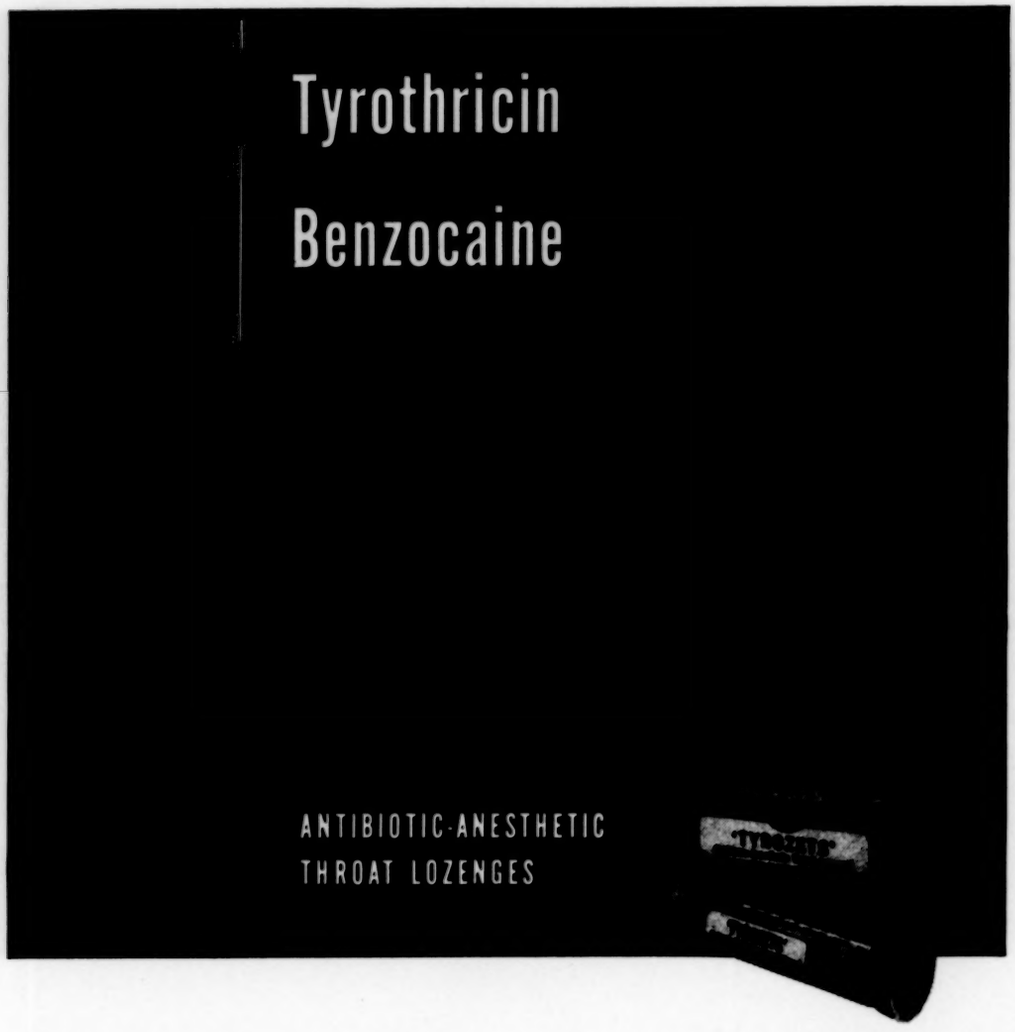
Characteristic of the normal adult vagina is the pH which ranges between 3.8 and 4.4. This acid level is resistant to pathogenic bacteria, protozoa and fungi. In such a medium the Döderlein bacillus flourishes and aids in the production of lactic acid.

FLORAQUIN — a product of Searle Research — aims at restoring and maintaining a vaginal environment inimical to the growth of pathogenic flora. Floraquin not only contains Diodoquin-Searle (5, 7-diiodo-8-hydroxyquinoline) but also supplies adequate lactose, dextrose and boric acid for reestablishing a normal vaginal pH; therefore, a normal vaginal physiology.



Tyrothricin, potent antibacterial extract of Dubos' bacillus, and widely considered the topical antibiotic of choice, is the principal ingredient of TYROZETS Lozenges, Sharp & Dohme's remarkable new preparation for prophylaxis and treatment of gram-positive throat and mouth infections, and for post-surgical care of the pharynx.

Tyrothricin is penetrating, nontoxic when applied locally, and highly effective against such gram-positive organisms as Corynebacterium diphtheriae, pneumococci, streptococci and staphylococci frequently responsible for infections of throat and mouth.

Each TYROZETS lozenge contains tyrothricin, 1 mg., and 5 mg. of soothing, analgesic benzocaine.

TYROZETS Antibiotic-Anesthetic Throat Lozenges rapidly relieve the pain and discomfort of infected or irritated throats, promptly destroying gram-positive pathogens. These new, nontoxic, pleasantly flavored Sharp & Dohme lozenges are indicated for treatment of gram-positive throat and mouth infections, sore throats, and especially following tonsillectomies and pharyngeal surgery. They are also effective for prophylactic throat protection when colds are prevalent.

TYROZETS Antibiotic-Anesthetic Throat Lozenges are packed in moisture-proof, plastic-stoppered tubes of 12.

SHARP & DOHME **TYROZETS**

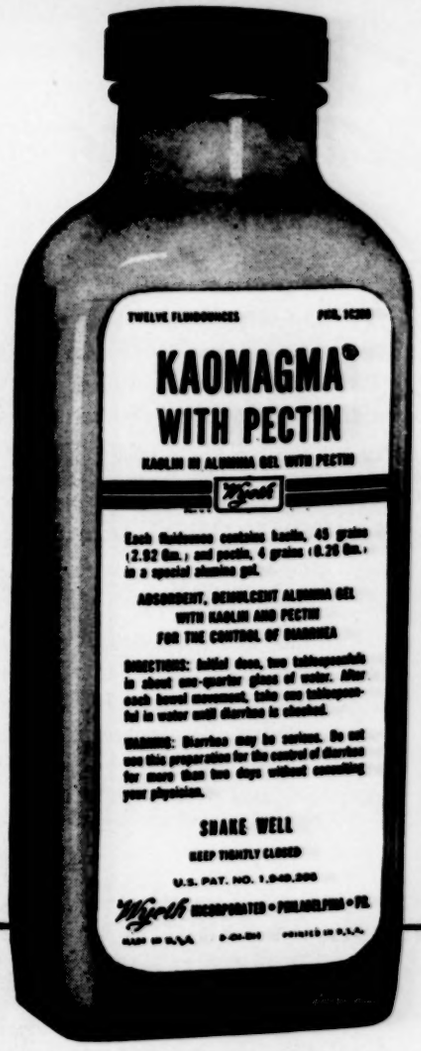
A New Product for Diarrhea based on Alumina

A practical and singularly effective alumina gel has been developed for its demulcent properties—to soothe and protect intestinal mucosa inflamed during diarrhea.

Other active ingredients are pectin and colloidal kaolin. Since the alumina gel is non-absorbable, it holds the kaolin and pectin in suspension—thereby increasing their effectiveness.

This unique product, Kaomagma with Pectin, quickly controls diarrhea—consolidates liquid stools, checks fluid loss, adsorbs bacteria and their toxins, and restores the patient's comfort.

It is free-flowing and has an entirely new taste especially acceptable to children.



Wyeth

PHILADELPHIA 3, PA.

Candy

FOR PRIMING PSYCHOGENIC AND SOMATIC PROCESSES

ALTHOUGH adequate to a nicety, meals can readily lose much of their nutritional function unless prepared and served for gustatory appeal. Drab meals may be refused, denying the patient the benefit of needed nutrients and calories. By virtue of variety of form, color and flavor, candies on the meal tray bring many welcome surprises of satisfaction. Their very presence sets psychogenic and somatic processes into operation which are beneficial to appetite, digestion, and the nutritional state. Rich in concentrated caloric energy and superlative in tastefulness, morsels of candy may give the needed psychogenic therapeutic impulse to inflect upwards the curve of recovery.

Candies are prepared with many valuable foods—milk, butter, eggs, fruits, and nuts. To the extent these foods are present, candies provide biologically adequate protein, appreciable amounts of the important minerals calcium, phosphorus, and iron, and B complex vitamins. Thus candies deserve recommendation whenever the clinical situation at hand permits this gustatory and psychogenic treat.

COUNCIL ON CANDY OF THE NATIONAL Confectioners' ASSOCIATION

1 NORTH LA SALLE STREET • CHICAGO 2, ILLINOIS

For a lady in distress

'Dexedrine' Sulfate relieves much of the distress of the menopause... by reawakening the patient's optimism and mental alertness ...by restoring her feeling of energy and well-being... by reviving her interest in life and living.

Unlike d-desoxyephedrine, 'Dexedrine' produces a uniquely "smooth" anti-depressant effect. It can be depended upon to improve the mood and brighten the outlook without giving the patient the uncomfortable feeling of "drug stimulation".

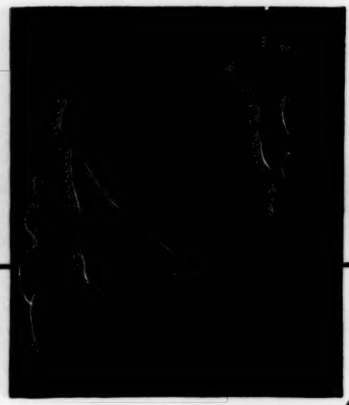
Dexedrine* Sulfate Tablets & Elixir

The anti-depressant of choice in the menopause

Smith, Kline & French Laboratories, Philadelphia

*T. M. Reg. U. S. Pat. Off. for dextro-amphetamine sulfate, S.K.F.

Hope for the "pelvic cripple"...



Chronic inflammation of the adnexa resulting in a fixed uterus, enlarged tortuous tubes with induration of the broad ligaments presents a therapeutic challenge to the physician.

In the treatment of chronic salpingitis and its sequelae, Jacobson's Solution produces objective evidence of improvement as well as subjective relief of pain and discomfort.

Diminution in size or disappearance of inflammatory masses has been noted even in cases refractory to other types of therapy. Both pharmacological and clinical studies have shown that its use produces increased vascularization—thereby establishing optimal conditions for the reduction of inflammation and absorption of exudate.

On this sound basis of pharmacological evidence and clinical effectiveness, Jacobson's Solution presents a therapeutic answer to an old problem—the chronically inflamed female pelvis.

Jacobson's solution

Available in 1 cc. ampules in boxes of 12 and 50.

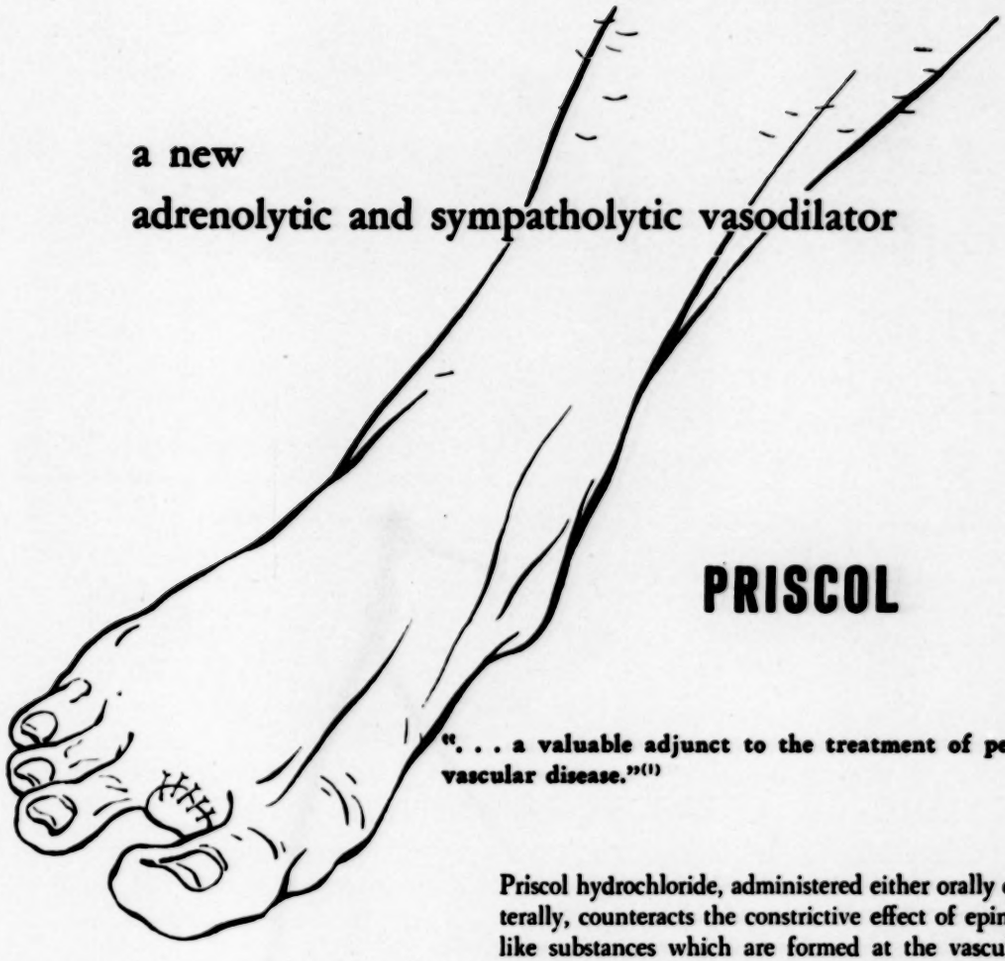
Painless upon administration and non-toxic.

HOW ADMINISTERED

Optimal results are obtained by a daily intramuscular injection of 1 cc. for 12 consecutive days. When this is not feasible, a minimum of 3 injections per week for four weeks should be given. Course may be repeated after an interval of 7 to 10 days.

For samples and literature, please address

E. Fougera & Company, Inc. • 75 Varick St • New York N Y



a new
adrenolytic and sympatholytic vasodilator

PRISCOL

". . . a valuable adjunct to the treatment of peripheral vascular disease."[1]

Priscol hydrochloride, administered either orally or parenterally, counteracts the constrictive effect of epinephrine-like substances which are formed at the vascular myoneural junction.

Priscol therefore produces circulatory improvement in many cases of Raynaud's disease, Buerger's disease, diabetic gangrene, and arteriosclerotic peripheral vascular disease.

Patients should be closely observed until optimal dosage is established since paradoxical effects or orthostatic hypotension may occur.

Issued: Tablets of 25 mg.; bottles of 100 and 1000.
10 cc. Multiple-dose Vials, each cc. containing 25 mg.

1. Grimson, K. S., Marzoni, F. A., Reardon, M. J., and Hendrix, J. P.: *Surg.*, 23:728, 1948.

• Complete information may be obtained from

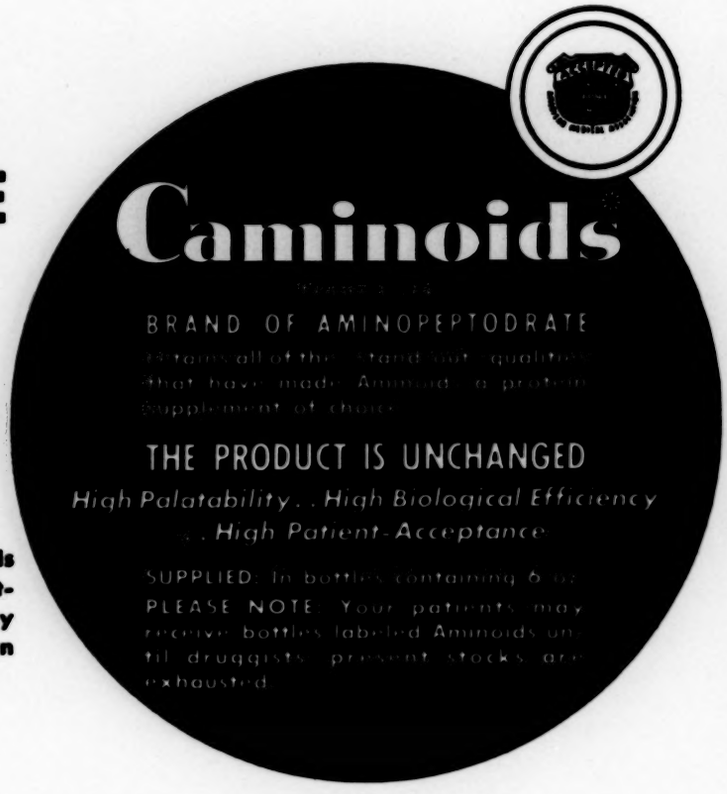
CIBA PHARMACEUTICAL PRODUCTS, INC., SUMMIT, NEW JERSEY

Ciba

2/1377M

PRISCOL (brand of benzazoline) Trade Mark Reg. U. S. Pat. Off.

NEW NAME for a TOP FAVORITE in Protein Nutrition



***New designation of Aminoids adopted as a condition of acceptance by the Council on Pharmacy and Chemistry of the American Medical Association.**

Arlington

THE ARLINGTON CHEMICAL COMPANY • YONKERS 1, NEW YORK

Tales and Details

During my calls these days, every time I mention Hypercillin*—the conversation begins to sound like a quiz program. It all starts when I lay this announcement on the doctor's desk—"Procaine penicillin has a new coat . . . and it's a slicker!"

Right away they want to know what a 'slicker' has to do with blood levels. The details go like this:

Hypercillin contains 300,000 units per cc. of 120 mgm. procaine penicillin G crystals, dispersed in fluid sesame oil with 2% aluminum monostearate, to delay absorption. This dispersing agent 'coats' the crystals, holding them in suspension for prolonged periods—and making smoother injections by cutting down needle plugging.

After injection—considerably less painful because of the procaine—the 'coated crystals' (water-proofed in their slickers) act as oily globules in a watery environment, where they are slowly absorbed. Absorption takes place around the periphery of the globule, and the procaine penicillin salt is slowly released into the blood—for therapeutic levels of at least 24 hours.

Hypercillin has two more factors of importance. The crystal size is large enough to maintain prolonged adequate levels—yet small enough to clear an 18-20 gauge needle without plugging. Sesame oil—the suspending medium—has these clinically established advantages: (1) less irritating to tissue; (2) less antigenic; (3) more suitable physically and chemically as a suspending medium.

Cutter Hypercillin offers a suspension of crystalline procaine penicillin G dispersed in sesame oil with 2% aluminum monostearate.

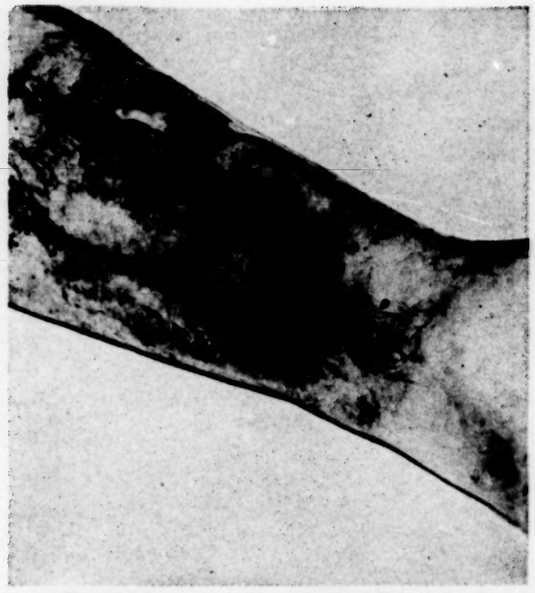
So you see why so many of my physicians are trying Hypercillin—and are agreeing "it's a slicker!"

Your CDM

(Cutter Detail Man)

**Trade Name for Cutter Procaine Penicillin G in Sesame Oil with 2% Aluminum Monostearate*

Cutter Laboratories • Berkeley 1, Calif.



Chronic, traumatic osteomyelitis of several years' duration—extremely malodorous and painful. This is one of hundreds of cases in which the prompt healing induced by Chloresium was reported by well-known clinics.

After treatment with Chloresium Ointment by packing on alternate days for six weeks. This followed "cleaning-up" of infection and malodor by continuous wet dressings of Chloresium Solution (Plain) for initial period of 48 hours.

CHLOROPHYLL HEALED

when other methods of treatment failed

● The case shown above is typical of hundreds, which proved stubbornly resistant to treatment until Chloresium therapeutic, *water-soluble* chlorophyll preparations were used. And the record* shows that an overwhelming majority of them not only responded rapidly to chlorophyll therapy, but healed completely in a relatively short time.

Try Chloresium on your slowest healing case

We invite you to try Chloresium Ointment or Solution (Plain) on your most resistant case—some ulcerative lesion, chronic osteomyelitis, wound, burn, dermatitis, or any other condition which calls for accelerated healing. Just mail the coupon at right.

Chloresium

***Natural, nontoxic therapeutic chlorophyll preparations*—Accelerates healing • Stimulates normal cell growth • Controls superficial infection • Reduces scar formation • Nontoxic, bland and soothing • Deodorizes malodorous lesions.**

Ethically promoted—At leading drugstores

*Boehme, E. J.	The Treatment of Chronic Leg Ulcers	The Lahey Clinic Bulletin, 4:242 (1946)
Bowers, Warner F.	Chlorophyll in Wound Healing and Suppurative Disease	Amer. J. Surgery, LXXIII: 37 (1947)
Cady, Jos. B. and Morgan, W.S.	Treatment of Chronic Ulcers with Chlorophyll	Amer. J. Surgery, LXXV: 4 (1948)
Johnson, Harold M.	Dermatologic evaluation	Arch. Dermat. & Syph. 57:348 (1948)
Langley, W. D. and Morgan, W.S.	Chlorophyll in the Treatment of Dermatoses	Penn. Med. Journal, Vol. 51: No. 1 (1947)
Rafsky, Henry A. and Kreiger, Charles I.	Treatment of Intestinal Diseases with sols. of W. S. Chlorophyll	Rev. Gastroent Vol. 15:549 (1948)

NEW—Chloresium Tooth Paste and Dental Ointment now make chlorophyll therapy available for the treatment of Vincent's infections and other periodontal diseases.

FREE—MAIL COUPON

RYSTAN CO., INC. Dept. JM-7
7 N. MacQuesten Pkwy., Mt. Vernon, N. Y.

I want to try Chloresium on my most resistant case. Please send me, without obligation, clinical samples and complete literature.

*Dr.*_____

*Address*_____

*City*_____ *Zone*_____ *State*_____

there's a better antitussive narcotic in

New, Pleasant Tasting

MERCODOL®

ANTITUSSIVE SYRUP

featuring **MERCODINONE ®** an improved, more potent narcotic — superior in cough control to codeine and heroin, but notably free from nausea, constipation or retention of sputum.

plus **NETHAMINE ®** a bronchodilator to relax plugged bronchioles.

SODIUM CITRATE a better expectorant to liquefy secretions.

EXCELLENT TASTE • WIDELY COMPATIBLE

Dosage: Adults, 1 teaspoonful; children ¼ to 1 teaspoonful. Repeat every 3 hours and as needed at night. *An Exempt Narcotic*, available at prescription and hospital pharmacies.

MERRELL

THE WM. S. MERRELL COMPANY · CINCINNATI, U.S.A.

Coming!

Relative Infectivity of Blood and Cerebrospinal Fluid in Secondary Syphilis
CHESTER N. FRAZIER and H. C. PIAN, Boston

Endocrinopathies Associated with Hyperostosis Frontalis Interna
FLOYD E. HARDING, Los Angeles

Sponge Biopsy in Cancer Diagnosis SIDNEY A. GLADSTONE, New York

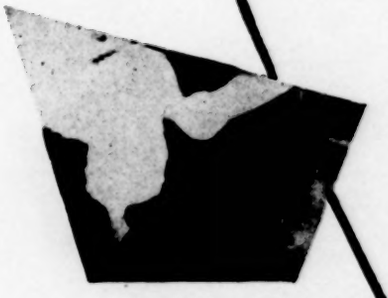
Treatment of Thromboangiitis Obliterans
WILLIAM J. MESSINGER, EDMUND N. GOODMAN and JAMES C. WHITE, Boston

Influence of the Serum Potassium and Other Electrolytes on the Electrocardiogram in Diabetic Acidosis
CARL S. NADLER, SAMUEL BELLET and MARY LANNING, Philadelphia

CRYMONASE

a specially processed whole defatted duodenal substance

Clinically effective in NON-SPECIFIC ULCERATIVE COLITIS



52 patients followed for more than a year showed marked improvement.[1,2]

- **Improvement commenced in 3-5 weeks.**
- **Frequency of bowel movements diminished.**
- **Stool consistency increased.**
- **Gross blood and mucus disappeared.**
- **Sigmoidoscopic evidence of mucosal healing followed symptomatic improvement.**

CRYMONASE

Clinical investigations, based on the hypothesis that non-specific ulcerative colitis is the result of a deficiency of an intrinsic protective factor normally present in the intestinal mucosa, showed dramatic responses following the oral administration of CRYMONASE.

CRYMONASE is a new specially processed duodenal substance whose chief action is the reduction of secretions of the gastro-intestinal tract and a decrease in motility. Special processing prevents autolysis of the substances normal to the raw tissues and they are retained in their natural state. *Supplied*—Tablets: Bottles of 100, 250, 500, 1000; Powder: 4 oz. bottle by weight.

IRWIN, NEISLER & CO. Decatur, Illinois

1. Friedman, M. H. F., Haskell, B. F., and Waldron, J. M.: Fed. Proc. 7:201, 1948.
2. Grossman, M. I.: Personal Communication (report to be published).

[redacted]

FLAT SPRING DIAPHRAGM

Physician's package and complete description of the *New Technique* will be sent upon request.

Ethically promoted—
Advertised only to the
medical profession.

Accepted by the Council on Physical Medicine of the American Medical Association.

Easily Fitted—The Lanteen Flat Spring Diaphragm, collapsible in one plane only, is easily placed without an inserter.

Remains in Position—The flat spring rim of the Lanteen Diaphragm gently but firmly holds the diaphragm in place even during changes in body position.

Long Lasting—Lanteen Diaphragms, made of the finest rubber, are guaranteed against defects for a period of one year.

Lanteen

LANTEEN MEDICAL LABORATORIES, INC.

900 North Franklin Street, Chicago 10, Illinois

Penicillin Powder Inhalation 'midst all the comforts of home

Here's a simple, convenient device for penicillin powder inhalation therapy in home or office. It is the Aerohalor—a small plastic inhaler complete with attachments for oral or nasal inhalation. It is used with disposable Abbott Sifter Cartridges containing 100,000 units of finely powdered crystalline penicillin G sodium.

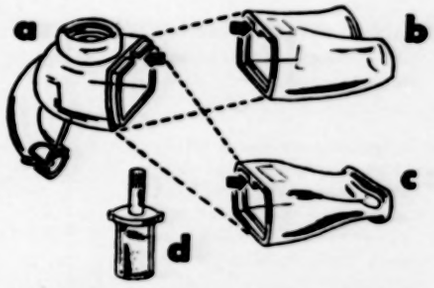
For oral inhalation, the patient attaches the mouthpiece, inserts a cartridge of penicillin powder and "smokes" the Aerohalor like a pipe. For nasal inhalation, the nosepiece is attached and the same procedure is followed. No tubes, valves or cumbersome machines are required, because the patient's respiration provides the necessary motive power.

This form of treatment is indicated for infections of the upper or lower respiratory tract produced by organisms susceptible to penicillin. It is contraindicated only for those infections not susceptible to penicillin and for patients allergic to the drug.

The Aerohalor and Abbott Sifter Cartridges are available at prescription pharmacies. Write for literature. ABBOTT LABORATORIES, NORTH CHICAGO, ILL.

the AEROHALOR
TRADE MARK

Abbott's Powder Inhaler



(a) Discharge chamber is attached either to (b) Mouthpiece or (c) Nosepiece for use with (d) Abbott Sifter Cartridge.

MODERN DIGITALIS THERAPY...

reduces dosage [redacted] *to milligrams*

... disability [redacted] *to hours!*

Simplicity of administration with dosage *by weight* and effect *in hours* —together with virtual freedom from locally induced nausea or vomiting —makes Digitaline Nativelle a preparation of choice wherever and whenever digitalis therapy is indicated.

In developing the first clinically-proven active principle of digitalis purpurea, Digitaline Nativelle has provided the medical profession with a major advance in the treatment of cardiac decompensation. Utilizing the active principle, Digitaline Nativelle acts uniformly whether administered by mouth or by vein.

Prescribed . . . for these 5 advantages:

1. Uniform potency by weight.
2. Identical dosage and effect when given intravenously or by mouth.
3. Virtual freedom from gastric upsets and other untoward side effects.
4. Absorption and action is rapid, uniform, determinable by the clock.
5. Active principle enthusiastically accepted by leading cardiologists.

SIMPLICITY OF ADMINISTRATION

RAPID DIGITALIZATION . . . *1.2 mg. in equally divided doses of 0.6 mg. at three-hour intervals.*

MAINTENANCE: *0.1 or 0.2 mg. daily depending upon patient's response.*

CHANGE-OVER: *0.1 or 0.2 mg. of Digitaline Nativelle may advantageously replace present maintenance dosage of 0.1 gm. or 0.2 gm. of whole leaf.*

Supplied through all pharmacies in 0.1 mg. pink tablets and 0.2 mg. white tablets — in bottles of 40 and 250. In ampules of 0.2 mg. (1 cc.) and 0.4 mg. (2 cc.) — in packages of 6 or 50. VARICK PHARMACAL CO., INC. (Division of E. Fougera & Co., Inc.) 75 Varick Street, New York, New York.

Digitaline Nativelle

. . . active glycoside of digitalis purpurea

(*digitoxin*)

[redacted]

Completely non-toxic anion exchange resin

PEPTIC ULCER THERAPY

An insoluble anion exchanger, RESINAT is unique in that it is in itself chemically inert, yet it normalizes gastric acidity and inactivates pepsin without disturbing the acid-base balance of the patient.

RESINAT is completely non-toxic. It does not cause constipation or diarrhea, cannot produce alkalosis; does not rob the system of chloride or phosphate ions.

Although 2 or more 0.25 Gm. RESINAT capsules every 2 hours usually provide satisfactory relief in acute or chronic peptic ulcer, larger doses may be necessary in some cases. In such instances, RESINAT Powder, available in individual 1 Gm. glassine packets, is the preferred dosage form—one packet (1 Gm.) stirred quickly in water, milk or other liquid, administered every 2 hours or as required.

Since RESINAT is non-toxic even in massive doses, the physician may feel free to increase the dosage until the patient reports satisfactory relief. Thereafter, dosage may be gradually reduced to a maintenance level.

[redacted]

HOW SUPPLIED:

Resinat Capsules (0.25 Gm.) in bottles of 50, 100, 500 and 1000

Resinat Powder (1 Gm. packets) in boxes of 50 and 100

(on prescription only)

THE NATIONAL DRUG COMPANY, PHILADELPHIA 44, PA.

MANUFACTURERS OF PHARMACEUTICAL, BIOLOGICAL AND BIOCHEMICAL PRODUCTS FOR THE MEDICAL PROFESSION.

"... created equal"

All infants are created equal in that vitamin adequacy is indispensable for their optimal health, growth and development through childhood and adolescence.

And all Zymadrops* are created equal in that each bottle uniformly and dependably provides *all these essential vitamins* in potent, concentrated drop-dosage form. The Upjohn manufacturing process *blends and disperses* both fat-soluble and water-soluble vitamins in Zymadrops for optimal stability, palatability and absorbability.

*Trademark, Reg. U.S.P.-N. Off.

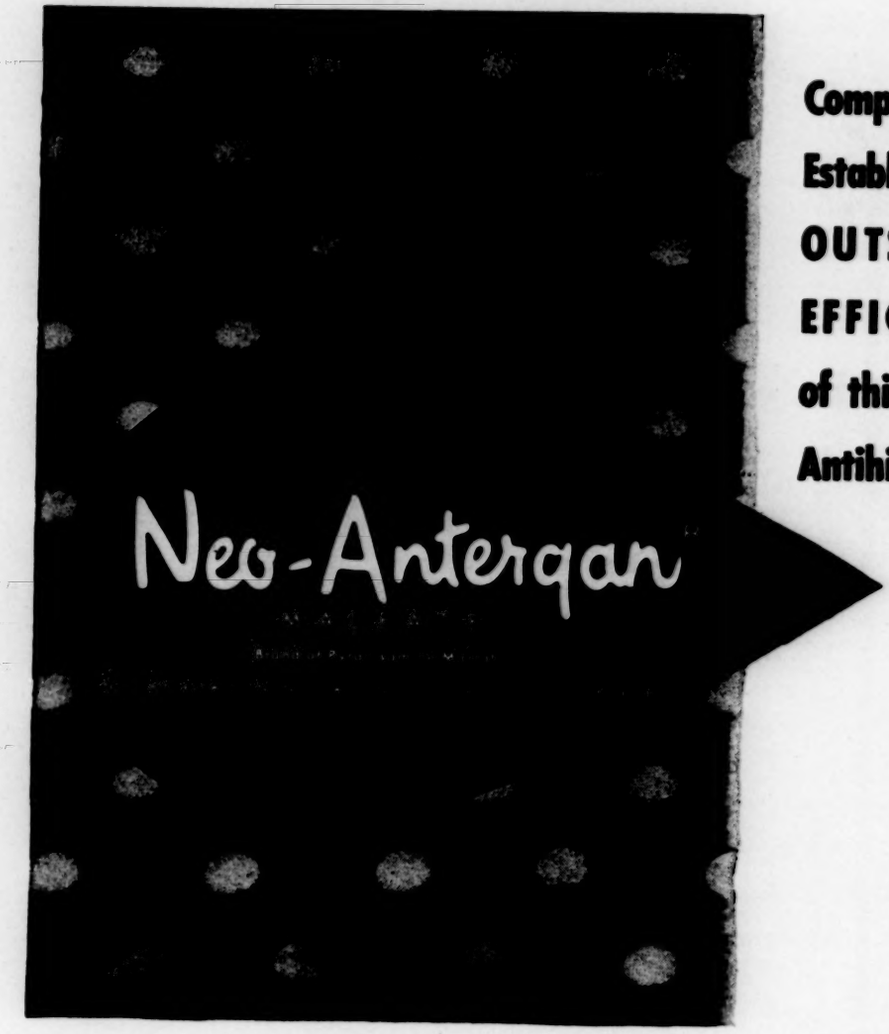
Zymadrops

Each 0.6 cc. contains:

Vitamin A	5,000 U.S.P. units
Vitamin D_3	1,000 U.S.P. units
Thiamine Hydrochloride (B_1)	1.0 mg.
Riboflavin (B_2, G)	1.0 mg.
Pyridoxine Hydrochloride (B)	0.5 mg.
Calcium Pantothenate	3.0 mg.
Nicotinamide	10.0 mg.
Ascorbic Acid (C)	60.0 mg.
Alcohol	2%

Upjohn

FINE PHARMACEUTICALS SINCE 1886



Comparative Studies Establish the OUTSTANDING EFFICACY of this Antihistaminic

Quantitative studies to determine the relative efficacy of six leading antihistaminic compounds have demonstrated that Neo-Antergan possesses a considerably greater protective power against histamine than do any of the other antihistaminic drugs tested.*

**Friedlaender, A. S., and Friedlaender, S., Correlation of experimental data with clinical behavior of synthetic antihistaminic drugs. Paper read before Fourth Annual Session, American College of Allergists, New York City, March 12, 1948.*

Your local pharmacy stocks Neo-Antergan in 25-mg. and 50-mg. tablets, supplied in packages of 100 and 1,000.

MERCK & CO., Inc. *Manufacturing Chemists* RAHWAY, N. J.

"RESULTS HAVE BEEN SO GRATIFYING . . . *that there appears to be little occasion for change.*"[1]

This is the opinion shared by many clinicians who have used **INTRADERM* TYROTHRICIN** in stubborn cases of acne vulgaris, sycosis vulgaris, furunculosis, impetigo, and other pyogenic skin infections.

INTRADERM TYROTHRICIN presents tyrothricin, most powerful antibiotic for local use, in a unique skin-penetrant vehicle permitting rapid diffusion of the medication throughout the affected area.

ADVANTAGES: Rapid and sustained antibacterial effect • Non-irritating to skin • Active even in presence of pus, serum, and exudates • Does not give rise to drug-fast strains • Leaves no unsightly film, making it most acceptable to patient.

1. Grinnell, E.: Journal-Lancet 68: 121 (Apr.) 1948.

*The word INTRADERM is a registered trademark of Wallace Laboratories, Inc.

INTRADERM TYROTHRICIN

SUPPLIED: 120 cc bottles containing 1 mg. of tyrothricin per cc

WALLACE LABORATORIES, INC.
53 Park Place **New York 8, N. Y.**